A Manual of the
COMMON CONTAGIOUS DISEASES

By

PHILIP MOEN STIMSON, A.B., M.D.

[illegible] *(Middletown), and St Francis (Poughkeepsie) Hospitals, President of St John's Guild (The Floating Hospital), Formerly, Attending Physician, The Willard Parker Hospital, and Director of the former Poliomyelitis Service of Knickerbocker Hospital*

and

HORACE LOUIS HODES, A.B , M D.

Pediatrician-in-Chief and Director of the Department of Pediatrics Mt Sinai Hospital, New York City, Clinical Professor of Pediatrics College of Physicians and Surgeons at Columbia University, Consulting Pediatrician North Shore Hospital, Formerly, Assistant in Pathology and Bacteriology Rockefeller Institute for Medical Research Associate Professor of Pediatrics Johns Hopkins Medical College and Director of Sydenham Hospital Baltimore

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Foreword

It is with great pleasure indeed that I announce the association with me in the authorship of A Manual of the Common Contagious Diseases, of Horace L. Hodes, M.D., Pediatrician-in-Chief and Director of the Department of Pediatrics of Mt. Sinai Hospital of New York City, and Clinical Professor of Pediatrics of The College of Physicians and Surgeons of Columbia University. An able teacher, a scholarly scientist, an experienced research worker, a talented clinician, he brings to the book wide experience and accepted authority.

In this edition he shares with me the responsibility for the many changes made throughout the book, necessitated in bringing the subject matter up-to-date. For possible future editions he will be the responsible editor and author.

PHILIP M. STIMSON

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Preface

Nine years have elapsed since the publication of the fourth edition of this text, years in which there have been many advances in the knowledge of the medical field covered. An extensive revision has therefore been necessary in the preparation of this new or fifth edition. Every chapter contains marked changes. In the chapter on antibiotics there has had to be considerable expansion due to the increase in number and knowledge of these valuable drugs in the last few years but otherwise efforts have been made not to increase the bulk of the volume.

Advances in bacteriology and virology have been described in connection with most of the diseases and special emphasis has been given to detailed present-day treatment. On the other hand, in the discussions of the pathology, clinical manifestations, complications, and differential diagnoses of the various illnesses, there has been only moderate modification. Scarlet fever is now described in a chapter on hemolytic streptococcal infections which are here discussed in considerable detail. Meningococcus meningitis now shares a chapter with other acute bacterial meningitides. Poliomyelitis has been again given a practically entirely new chapter, with an expanded discussion of the newer aspects of pathogenesis, prevention, and especially treatment. There are quite new discussions of viruses in general, of whooping cough vaccine, of parapertussis, of Rickettsialpox, of myocarditis in diphtheria and its treatment, of hospital management of contagion, and of many other items. There are new illustrations, charts, and tables. In particular, a large table of vaccines in the first chapter, and two about antibiotics in Chapter 3, should prove useful.

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Many items have been added to the bibliographies, and some have been dropped. The original threefold purpose of these bibliographies is preserved, *viz*, to include references of articles of historical value, articles referred to in the text, and articles of broad general interest, particularly if they have recent good bibliographies themselves.

On the other hand, with all the many changes, attempt has been made to retain that which had been found acceptable in previous editions, clarity and readability, handiness and compactness, but above all authenticity and integrity.

A number of people have given assistance in many ways: doctors, secretaries, friends and relatives, in all too many to mention To each and all we give our sincere thanks

In the preparation of a book like this, two heads are always better than one, two viewpoints are more stabilizing; two minds more apt to avoid mistakes. The association in this work has been most enjoyable, we hope the product is found worthy of the effort

PHILIP M. STIMSON, M D

HORACE L. HODES, M D

NEW YORK, N Y

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SUMMARY OF THE COMMON CONTAGIOUS DISEASES (Inside Back Cover)

Common Contagious Diseases

1

Principles of Contagion

In presenting the manifestations of the common contagious diseases, it is well first to discuss briefly the general theories of infection and immunity, particularly from the clinical aspect

Contagious diseases are infectious diseases that are spread or contracted as the result of contact with specific infectious material It is not necessary to have an intermediate host, such as a mosquito, in which the infectious agent may undergo certain changes or stages of development On the other hand, infectious diseases embrace all the diseases that are caused by living transmissible agents, whatever the means of transmission, and are abnormal conditions resulting from harmful local and general interactions between a host and an invading parasite with consequent change in tissues and symptoms Thus all contagious diseases are infectious diseases But although all infectious diseases are communicable, some, such as malaria and yellow fever, are not so by simple contact, hence they are not contagious The communicable or infectious diseases which are contagious include the following:

Common colds, influenza, pneumonia, tuberculosis

Acute conjunctivitis, trachoma

Gonorrhea, syphilis, leprosy, puerperal sepsis, erysipelas, impetigo, epidemic encephalitis

Chickenpox, smallpox, measles, rubella, scarlet fever, diphtheria, Vincent's angina, mumps, whooping cough, meningococcus meningitis, poliomyelitis

Although the first three groups might well be considered common diseases, only the last group is discussed in this manual. Of these, scarlet fever, diphtheria, Vincent's angina, whooping cough, and meningococcus meningitis are due to specific bacteria. The others are generally believed due to specific viruses.

Viruses.—The exact nature of these agents of disease is unknown They may be microörganisms that have evolved by degeneration from larger microörganisms, many of them probably from bacteria. They are not necessarily all of the same nature Some, at least, are crystalline proteins. They survive by biological reproduction, and by transfer from one host to another They have certain characteristics in common and they can be differentiated from each other by certain other characteristics and faculties. Of the characteristics in common:

Viruses are filterable, being much smaller than ordinary bacteria They vary in size from 8 to 250 millimicrons in diameter, the virus of poliomyelitis being one of the smallest and that of vaccinia one of the largest. Most viruses cannot be visualized with the best microscopes, but, under certain conditions some of them can be made to appear as "elementary bodies," as in vaccinia, smallpox, fowl pox and psittacosis, and they may produce characteristic small intracellular entities known as inclusion bodies which have diagnostic significance; *e.g.*, Negri bodies in rabies By the electron microscope, viruses can be readily visualized as having characteristic sizes and shapes

Viruses are obligate parasites in that they grow only in living cells. Under proper circumstances they are capable of abundant multiplication or reproduction. Various viruses, such as those of vaccinia, influenza, measles, and mumps, have been cultivated in living chick-embryo tissue and the three types of poliomyelitis viruses on various human and monkey embryonic tissues and on monkey kidney cells.

Viruses for the most part die quickly outside a human host unless preserved in some special manner, but the viruses of

at least smallpox, vaccinia, fowl pox and psittacosis withstand drying and when dry may remain active a number of days unless exposed to ultra-violet light which readily destroys them. Fifty per cent glycerine will preserve many viruses although it kills bacteria. Certain viruses survive freezing, in fact a temperature of below 4° C. is essential for the proper preservation of vaccine virus.

Viruses may be divided roughly into the following classes according to the type of tissue they are most likely to infect.

I. Epitheliotropic: as in warts, herpes labialis, trachoma
II. Viscerotropic: as in smallpox, yellow fever, measles
III. Pneumotropic: primary: as in psittacosis, influenza
secondary: as in measles, smallpox.
IV. Neurotropic
1. Epidemic, as in poliomyelitis, certain encephalitides
2. Non-epidemic, as in rabies, herpes zoster
3. Post-infectious, as in measles, mumps, vaccinia

Viruses cause diseases which, as a rule, are followed by a lasting immunity, the immunity probably being both cellular and humoral. Most virus infections have longer incubation periods than do those caused by bacteria, influenza and herpes being exceptions. Virus diseases in man are for the most part more contagious than the bacterial diseases, of the latter whooping cough being a notable exception, and as far as is known, the spread of the majority of the virus diseases of man apparently results from contact by means of droplet infection.

Viruses can be inactivated by specific sera. In most instances, immunity to a virus disease has not been obtained by vaccination with inactive or dead material. However, the vaccine now used for protection against equine encephalomyelitis and the Semple rabies' vaccine contain no demonstrable quantity of active virus. As now marketed, the same can be said to be true of the Salk poliomyelitis vaccine. A living virus, modified by generations of growth away from man is used for immunization against smallpox and the

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vaccine for yellow fever is also a living but attenuated virus. In general, the administration of a killed virus vaccine will not give protection for more than six to twelve months, while the immunity obtained from a living but attenuated virus vaccine is comparable to that obtained from an attack of the disease in question in that it usually lasts for a number of years.

In no virus disease after the onset of clinical manifestations has an antiviral serum proved to have curative properties. Viruses multiply inside tissue cells where, once established, they cannot be reached by an antiserum and Rivers has stated that by the time the signs and symptoms of infection are manifest, all of the cells that are going to be infected in that particular host have already been entered.

The usual response in the blood to a virus infection is by lymphocytes with a normal or depressed total leukocyte count. The sedimentation rate also is usually normal at

cessfully by antibiotics Chloramphenicol (chloromycetin) and the tetracycline group of drugs are effective in the treatment of lymphogranuloma venereum and psittacosis, and these antibiotics also appear to have a favorable action in some cases of atypical pneumonia

Immune serums given during the incubation period can prevent or mitigate certain blood-borne virus infections such as measles and infectious hepatitis, and with much less effectiveness, mumps and perhaps rubella and poliomyelitis

Viruses can also be differentiated from each other by the clinical and pathological conditions they produce, by immunological reactions such as inactivation with specific antisera, and by the type of hosts attacked. For instance, the

virus of measles will cause measles only, is inactivated only by the serum of a person immune to measles, and will attack only man and certain monkeys.

Of the five common virus infections of children, measles and rubella, chickenpox, small pox and mumps, the individual viruses are alike in that all strains of each of these viruses are antigenically similar. In each disease one cannot distinguish by serological means between strains of virus isolated from different outbreaks. Primary infection takes place in the respiratory tract and is followed by a long incubation period. These diseases are blood-borne infections in which the virus spreads in the blood stream so as to reach the tissues where the characteristic lesions develop. Antibodies are formed which neutralize the virus, that is, in their presence the virus cannot infect cells. These antibodies usually persist for many years if not for life, so that true second attacks of these diseases are very rare.

Influenza and poliomyelitis are similar infections to the above in running a rapid course usually followed by elimination of the virus, but there is little or no cross immunity between types of the same virus so that theoretically at least, second attacks may occur at any time without any modification by a previous attack. The influenza virus can spread on the surface of the respiratory tract without coming in contact with antibodies in the blood stream so that clinical manifestations can develop despite these antibodies. Similarly the poliomyelitis virus can survive and grow in the alimentary canal despite antibodies in the blood stream.

Certain virus infections of a pregnant woman affect the fetus and others do not. Apparently the rubella virus is the only one that frequently acts in early pregnancies to cause cataracts or other defects but the influenza virus can kill the young fetus. The viruses of measles, chickenpox, and poliomyelitis apparently do not similarly affect the unborn baby and that of mumps seldom does, but babies shortly before birth have been infected with measles and chickenpox by their mothers, and Schick has reported pock-marked babies

vaccine for yellow fever is also a living but attenuated virus In general, the administration of a killed virus vaccine will not give protection for more than six to twelve months, while the immunity obtained from a living but attenuated virus vaccine is comparable to that obtained from an attack of the disease in question in that it usually lasts for a number of years.

In no virus disease after the onset of clinical manifestations has an antiviral serum proved to have curative properties Viruses multiply inside tissue cells where, once established, they cannot be reached by an antiserum and Rivers has stated that by the time the signs and symptoms of infection are manifest, all of the cells that are going to be infected in that particular host have already been entered.

The usual response in the blood to a virus infection is by lymphocytes with a normal or depressed total leukocyte count The sedimentation rate also is usually normal at least in the early stages

All drugs and antibiotics are ineffective against the smaller viruses, but several viruses of large size may be treated successfully by antibiotics Chloramphenicol (chloromycetin) and the tetracycline group of drugs are effective in the treatment of lymphogranuloma venereum and psittacosis, and these antibiotics also appear to have a favorable action in some cases of atypical pneumonia

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As for diagnosis, specific complement fixation and neutralization tests for certain virus infections such as poliomyelitis, mumps, lymphocytic choriomeningitis, and certain of the encephalitides are now available.

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of the bacteria and are liberated upon the disintegration of the bacteria.

To exert their toxic effects, toxins must enter into a chemical combination with cells, hence there is a necessary period of incubation before symptoms of their activity appear. From the clinical viewpoint, toxins have two major features The first is the toxic property which causes many of the manifestations of the various contagious diseases such as the neuritis and myocarditis in diphtheria, and the exanthem in scarlet fever. This property may also serve a useful purpose, as when used in the Schick and Dick skin tests for susceptibility. The second feature of a toxin is that it possesses the property of stimulating in human beings and certain animals the production of a resistance to it, that is, of an antitoxic property or antitoxin, demonstrable in the blood serum. The horse, being extremely susceptible to all toxins, in the chief source of the commercial production of antitoxins The toxins of the contagious diseases are not absorbed from the alimentary tract but act only when injected parenterally or when produced during an active infection.

Besides toxins, the other agency of importance by which bacteria act to cause disease is bacterial proteins, mostly nucleoproteins, of which the greater part of the bodies of bacteria is made up. The effects produced by these proteins are not specific, but are more or less toxic and pyogenic in power, as are many foreign proteins when introduced into the circulation of animals

These offensive powers of bacteria vary according to several factors First, the disease-producing power or virulence of the organism in question may vary enormously. Certain diphtheria bacilli have the power of producing an extremely poisonous toxin, while other true diphtheria bacilli may be able to produce little if any toxin The virulence of a particular germ may be increased by rapid passage from man to man, or from animal to animal, as happens sometimes in epidemics However, most epidemics are caused by an increase in the dosage of the infecting micro-

born of immunized mothers who were exposed to smallpox during their pregnancies. Thus viruses and also viral antibodies can cross the placenta.

INFECTION

The mere presence of bacteria and viruses in or upon the body of an individual constitutes contamination rather than infection It is not until the pathogenic agents have invaded and proliferated in the deeper tissues of the body that infection may be said to exist. Although infection may enter the body by any one of five different portals of entry, *i e.*, the skin, the respiratory mucous membranes, the alimentary tract, the urogenital tract, and before birth, the placenta, in the contagious diseases entry is nearly always *via* the respiratory mucous membranes. After the infecting organism has entered the body, certain of the causative agents have a selective tissue affinity, such as that of the mumps virus for the salivary glands, that of the meningococcus for the meninges and that of the smallpox virus for the whole person, yet all three infections usually enter by the upper respiratory tract

Viruses cause disease by their effect on the tissue cells in which they grow Thus in poliomyelitis they attack various nerve cells especially the motor cells in the anterior horns of the spinal cord and thus cause damage

Invading bacteria act to cause disease largely through certain properties, particularly toxins and bacterial proteins Bacterial toxins are poisons which are produced by bacteria as they grow, whether the growth be in living tissue or in artificial culture media Toxins are of two types exotoxins and endotoxins. Exotoxins, or extracellular toxins, exist outside the cell bodies of the microorganisms. For instance, when diphtheria bacilli are grown in broth and the broth is then filtered through a porcelain filter, the resulting filtrate contains no bacteria but does contain a powerful exotoxin Endotoxins or intracellular toxins are retained in the bodies

family Enterobacteriaceae (E. coli, Salmonellae, and Shigellae), and it has an *in vitro* neutralizing effect upon the viruses of mumps and influenza.

Of the *specific defensive forces*, there might be mentioned, first, phagocytosis, by which various leukocytes of the blood and certain tissue cells are enabled to engulf and destroy such foreign substances as bacteria The process of phagocytosis may be influenced by certain intangible properties, or antibodies in the blood, called bacteriotropins and opsonins.[1] There are also other types of antibodies which are in themselves defensive forces of resistance:

1. *Antitoxins*, which counteract the effects of soluble toxins These are the principal antibodies involved in natural and acquired immunity, and also in serum therapy However, therapeutic sera are of three types as to their activities: antitoxic, as for diphtheria, tetanus, and scarlet fever; antibacterial, as for pneumonia and meningococcus meningitis, and antiviral, as for measles

2. *Agglutinins*, which are those antibodies capable of causing clumping or agglutination of such forms of antigens as bacilli, so that the antigens thereby lose their motility and form clumps of agglutinated masses

3 *Precipitins*, which coagulate or precipitate soluble substances Bacteriolysins are somewhat different in nature, because they may not be in themselves destructive, but have the specific power of combining with bacteria and causing their lysis or destruction by bringing them into contact with a ferment-like complement, which by itself cannot act directly upon the bacteria Such an intermediary is called

[1] Antibod [illegible]

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organism in a susceptible population, the virulence being constant throughout the epidemic Occasionally the virulence can also be increased by growth in the presence of some other organism as for example when the diphtheria bacillus is grown in the presence of a streptococcus Virulence may be decreased, on the other hand, by prolonged growth on culture media with many transplantings. It may also be decreased or attenuated by aging or by the application of sublethal doses of heat or of chemicals. The process of attenuation was used, for instance, in Pasteur's preparation of rabies vaccine, where living but very weak rabies virus was used for stimulating the increase of the body's resistance

The offensive powers of bacteria vary, in the second place, in the number or dosage of the invading organism and in their path of entrance A third factor is the germ's own *defensive powers against the host's resisting mechanism.*

IMMUNITY

The host's resistance to infection, that is to say, his immunity, is the sum of the forces he can muster against infectious agents and their products, and is founded on specific and non-specific defensive forces.

Of the *non-specific defenses* may be mentioned the mechanical obstacle to invasion offered by an intact mucous membrane or epithelium Furthermore, mechanical forces, such as the production of mucus by the mucous membrane, help to wash away contaminating bacteria, and an even more powerful factor is the active antiseptic property present in certain bodily juices, such as the saliva and the gastric juice.

Several years ago it was discovered that there is present in the plasma of man and animals a euglobulin which is part of the natural defense mechanism. This substance, which has been named "properdin," is not an antibody, but the presence of complement (the C'3 fraction) is necessary for its action. Properdin appears to be of great importance in the natural resistance against Gram-negative bacteria of the

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[1] Antibodies may be defined as specific constituents of the blood and tissue fluids produced by the cells of a host in reaction against an antigen such as an infecting microparasite or its products. Antigens are substances that can cause the formation of antibodies in the blood and tissue fluids. For illustration, for the antigen "soluble bacterial toxins," the antibodies are antitoxins; for the antigen "soluble bacterial proteins," the antibodies are precipitins; for the antigen "bacteria," the antibodies may be agglutinins or bacteriolysins or opsonins. Utilizable antigens include bacterial and viral vaccines, tuberculins, toxins and toxoids. As a rule antigens and antibodies are not absorbed without change from the gastro-intestinal tract.

an amboceptor, and thus bacteriolysins may be bacteriolytic amboceptors

These defensive forces constitute immunity, which thus means resistance against infection due to parasites (such as bacteria and their products) which are able to cause disease in other animals of the same or different species. As a result of combinations of these defensive forces and of a number of other circumstances such as age, race, heredity, habitat, climate, weather, and sex, mankind may enjoy various types of immunity and immunities of varying degree or extent.

Immunity may be specific, that is, against a particular disease, or it may be non-specific, such as resistance to infection in general

Specific Immunity.—Specific immunity may be divided into two main types, natural and acquired.

NATURAL IMMUNITY —Natural immunity has been defined as the expression of an inherited equipment modified by favorable or unfavorable environmental influences. It is of several different kinds It may be related to species; for example, man is not susceptible to fowl cholera, distemper, and certain other animal diseases, it may be racial, of which the comparative immunity of the American Indians and the Eskimos to scarlet fever is an example, or it may be familial, for some families are relatively immune to scarlet fever and others relatively susceptible, or finally, it may be individual and dependent on such factors as age, sex, food, and inheritance.

ACQUIRED IMMUNITY —Acquired immunity is of two general types, active and passive

Active Acquired Immunity —An active immunity is acquired in three ways

1. A previous attack of a contagious disease, especially if due to a filtrable virus, is almost always followed by immunity, particularly if the incubation period and course of the disease have been long enough to allow the individual to be stimulated to produce his own antibodies for resistance against possible future infections of that disease. Because

diphtheria has a short incubation period and short course, particularly if treated early with serum, and because immunity to it is largely antitoxic, and antitoxins are produced slowly, it is followed in only 50 per cent of the cases by immunity at the end of the year. Very mild and therefore unrecognizable attacks of a disease such as occur in whooping cough and poliomyelitis also confer immunity. Pneumonia, the common cold, erysipelas, and gonorrhea are contagious diseases, one attack of which confers no immunity.

2. Repeated exposure without evident infection, the so-called subclinical inoculation, is responsible for most of the immunity of a general population to many of the endemic diseases. This is particularly true in respect to diphtheria and scarlet fever. Neither of these diseases is highly contagious. Virus diseases which are more easily communicated, such as small pox, chickenpox and measles, are almost invariably *contracted by susceptible contacts on the first exposure*, so that subclinical inoculations and the resulting immunity do not occur in these instances. Poliomyelitis is an exception to this. In countries with poor sanitation, infants, beginning while they still have a congenital immunity from their mothers, are exposed to the virus of this disease often enough to be stimulated to produce their own antibodies, so that the actual disease is rare among Filipinos. Even in countries where sanitation is good, most individuals become immune to poliomyelitis after exposure without suffering a clinically recognizable attack of the disease.

There is as yet no known way by which a deliberate exposure to any contagious disease can be so regulated as to be certainly insufficient to cause an infection but at the same time effective in stimulating resistance to that disease.

The development of immunity from repeated exposures varies in accordance with the opportunities for exposure. In congested areas with poor sanitation there are so many carriers of the causative organisms of the endemic diseases that the immunity of the bulk of the population is kept high

In rural districts there are comparatively few opportunities for exposure and accordingly there is a much greater susceptibility to most of the contagious diseases.

Certain individuals fail to become immune after an infection because they have a greatly reduced ability to form antibodies, due to a deficiency of serum gamma and beta-2 globulins. A congenital and an acquired type of agammaglobulinemia have been recognized. The congenital form appears to have a sex-linked inheritance pattern since all cases thus far reported have been males. The acquired form

TABLE 1.—SOME ACTIVE

Type	Disease	Description
I Bacterial vaccines	Whooping cough	Killed bacilli
	Typhoid fever	Killed bacilli 1 billion per ml
	Plague	Killed bacilli 2 billion per ml
	Cholera	Killed bacilli 8 billion per ml
	Tuberculosis	(B C G) attenuated bacilli
II Bacterial toxins	Diphtheria	Modified toxin { alum ppt alum hydrox fluid
	Tetanus	Modified toxin { alum ppt alum hydrox fluid
III Rickettsiae	Typhus	
	louse borne	Grown on egg-embryo, and killed
	flea-borne	None (?)
	Rockey Mountain spotted fever	Grown on egg yolk-sac (Cox) and killed
IV Viruses	** Influenza	Grown on egg-embryo and killed by formaldehyde
	** Mumps	Grown on egg-embryo and { killed attenuated
	Poliomyelitis	Grown on monkey kidney and killed by form (Salk)
	Rabies	Killed, rabbit cord prep (Semple)
	Small pox	*Modified by growth on calves
	* Yellow fever	Modified by growth on egg embryo

** Still of uncertain value
* By U S Navy or U S Public Health Service

of the disease occurs in both males and females. Agammaglobulinemia is accompanied by greatly increased susceptibility to bacterial infections. Resistance to viral infections is also affected, but to a lesser degree.

3. *Active immunity* may be acquired by means of vaccines. A vaccine is any substance the administration of which will stimulate a person (or animal) to produce his own immunity to a given disease. Thus it is an antigen used for active immunization. There are four different types of vaccines or prophylactic antigens. They are

IMMUNIZATION MATERIALS

		Administration		
Age	*Dosage*	*No.*	*Interval*	*Recall - Booster*
4-12 weeks	0.5 ml (total of 12 antigenic units)	3	2-4 weeks	After 1 yr., then 2-3
Before exposure	0.5 ml	3	1-4 weeks	Every 1-2 yrs. p.r.n.
Before exposure	0.5 and 1.0 ml for adults	2	1-3 weeks	Every 1-6 mos.
Before exposure	0.5 and 1.0 ml for adults	2	1-2 weeks	Every 4-6 mos.
1 wk. plus (if skin test negative)		1		None
3-5 mos. plus	0.5 ml	3	1 month plus	Every 3 yrs. in childhood and on exposure
3-5 mos. plus	0.5 ml	3	1 month plus	Every 4 yrs. in childhood and on exposure
Before exposure	0.25-0.5 ml	2	2-4 weeks	p.r.n.
10 plus days before exposure	0.5 ml	3	5-7 days	p.r.n.
Before exposure	1.0 ml	1		Annual (*)
Before exposure	1-2 ml	1		
Before exposure	1.0 ml	3	4 weeks and 7 months	Possibly annual
After exposure	2.0 ml	21	Daily	After 6 mos. on re-exposure
First year		1		Every 5 yrs. and on exposure
Before exposure	0.5 ml *	1		

(*a*) A virus such as an attenuated or weakened virus as in the Pasteur inoculations against rabies, or a virus modified by animal passage as in vaccinia There are also "killed" virus vaccines as that for equine encephalomyelitis, the Semple antirabies vaccine, and the Salk poliomyelitis vaccine.

(*b*) A preparation of killed bacteria, or a solution of bacterial proteins, such as typhoid and whooping cough vaccines

(*c*) A toxin, either by itself, as in scarlet fever, or modified by attenuation to form toxoid as in diphtheria and tetanus

(*d*) A preparation of killed rickettsiae, as in the vaccines against typhus fever, and Rocky Mountain spotted fever

In general, when toxoid or some other antigen is given intracutaneously, or in many injections, a greater percentage of people are immunized than when the antigen is given subcutaneously or in fewer injections with the same total dosage

At the present time, the preferred sequence of immunizations is the triple vaccine against whooping cough, diphtheria, and tetanus (alum precipitated or aluminum hydroxide adsorbed), given in three monthly injections beginning at about three months of age, vaccination against smallpox in the latter part of the first year of life, a recall or booster injection of the triple vaccine (without alum) at about 18 months, another injection two years later, and still another three years after that. The Schick test for diphtheria, vaccination for typhoid fever, and further booster injections against tetanus are done when indicated

Passive Acquired Immunity —Passive acquired immunity depends on defensive factors or antibodies, which do not originate in the person concerned, but are acquired passively by the receipt of serum from a person or animal that has acquired an active immunity to the disease in question

1 If a mother has had measles her baby is immune for the first four to six months of life. This congenital passive immunity is apparently transmitted *in utero* and is present irrespective of whether the baby is breast-fed or not. Similarly, depending on the mother's immunities, newborn babies

have a temporary congenital immunity also to the virus diseases rubella, mumps, chicken pox and apparently poliomyelitis and also an antitoxic immunity to diphtheria and to the erythrogenic toxin of beta-hemolytic streptococci which causes the rash of scarlet fever. Perhaps because of not yet being sensitized, they are also apparently immune for the first week to upper respiratory infections. They have no immunity, congenital or otherwise, to whooping cough and tuberculosis, gonorrhea, and syphilis, tetanus and erysipelas, alimentary infections and pyogenic infections.

2. The injection of a horse serum such as that containing diphtheria antitoxin into those who have been exposed to the disease gives them a passive immunity as long as this foreign serum is present in the circulation, or an average of about two weeks. Human serum remains in the human circulation longer, and immunity acquired from the injection of such a serum as human convalescent measles serum is thought to last from three to five weeks. Most antibodies in human serum are gamma globulins, and they can be separated from other serum components. Preparations of gamma globulin made by fractionation of human serum have been available for a number of years. One ml. of these preparations is equivalent in antibody content to about 25 ml. of whole serum.

Non-specific Immunity.—Non-specific immunity is influenced by many factors. It may be decreased by:

1. Fatigue, physical or mental, which has a very definite influence.

2. There is clear experimental evidence that endocrine factors may also be involved in resistance to infection. For example, large doses of cortisone render laboratory animals more susceptible to poliomyelitis viruses, the hormone favoring invasion and multiplication of these agents. There are also clinical grounds for believing that hormones, such as cortisone, may, in man, exert a markedly unfavorable influence upon the course of bacterial and virus infections. For

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CONTAGIOUS DISEASES

It will be noted that contagious diseases are those diseases which are caused by living transmissible agents, and are spread or contracted by contact. The stages of contagious diseases are as follows:

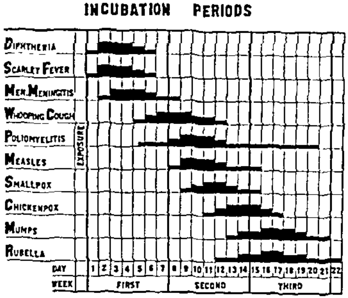


FIG. 1.—Showing the usual length in days of the incubation periods of ten common contagious diseases. It should be noted that the first four with the shortest incubation periods are the only bacterial diseases of this group, the lower six being caused by viruses.

First is the *incubation period,* which represents the time that elapses between the inoculation of the patient and the onset of symptoms. During this period the infecting microorganisms multiply and produce toxins, which in turn unite with or attack those organs or tissues with which they have a selective affinity. In general, incubation periods vary

instance, children under continuous cortisone treatment for asthma have died of concurrent chickenpox.

3 Chilling and exposure, and thus cold and damp weather. The climate also is of importance Certain hemolytic streptococcal infections are much less common in the tropics than in the temperate zones

4 Poor hygienic conditions, overcrowding, filth

5 Malnutrition, anemia and deficient diet, particularly the lack of vitamins, as in rickets.

6 The occurrence, present or recent, of some other infection For instance, scarlet fever predisposes to diphtheria, at least in hospitals

Tissue Immunity.—Whereas the antibodies concerned in the described forms of immunity are present in the natural fluids of the body, certain of the tissues themselves can become resistant to infection. Hence there are both humoral and tissue immunities Thus an area of the skin where there has recently been a minor infection or a heavy sun-tan may become resistant to the scarlet fever toxin and not be involved in an otherwise general scarlet fever eruption Schick has noted that healthy mothers, immunized to small pox by vaccination, have been exposed to the disease during pregnancies which produced pockmarked infants, suggesting that the mothers were protected by cellular or tissue immunity but had not enough humoral antibodies to prevent the virus *from passing from the mother's blood stream to the fetus in utero*

In poliomyelitis the spinal cord substance of a convalescent monkey inactivates potent virus but the cord of a normal monkey fails to do this, indicating that there has been some change in the properties of the cord tissues. When the poliomyelitis virus enters the nose and throat the secretions may contain enough humoral antibodies to neutralize it If this fails, and the virus penetrates to the central nervous system, should there be a tissue immunity this will act as a second line of defense.

people differ greatly in their immunity, there are all variations in severity of the various contagious diseases. In some people, antitoxic protection may be marked, but antibacterial protection low. Thus, for example, the scarlatinal streptococcus may be able to cause in certain individuals a severe throat infection, without such symptoms of absorption of the toxin as the rash in the skin. On the other hand, the infecting organism may be unusually virulent or the dosage of the infection may have been unusually large, and we then find the so-called toxic or malignant cases of diphtheria, meningococcus meningitis, and scarlet fever where the patient is overwhelmed from the onset.

THE EXANTHEMATA

This group of diseases includes smallpox and chickenpox, measles and rubella, scarlet fever and typhus fever. These diseases have in common an incubation period, prodromal symptoms, an exanthem and an enanthem (eruptions on the skin and mucous membranes respectively), and finally a desquamation, but typhus fever, while communicable only through the flea as intermediary, is therefore not contagious as are the others. The enanthem appears during the prodromal period and usually persists until the exanthem is fully out. It is of great diagnostic importance, particularly in measles and scarlet fever. The exanthem in each disease shows first as an erythema or congestion of the skin. This erythema ultimately becomes general in its distribution, but each disease has its selective area for first appearance. Measles, rubella, and smallpox usually show first on the face, chicken pox and scarlet fever on the trunk. With all of them the erythema spreads rapidly. The initial erythema may be macular or diffuse from the onset; when macular, it may rapidly become diffuse, or it may remain macular throughout its course. The coalescence of macules into diffuse areas may be general or in variously sized patches. The erythema varies both in intensity and duration in the dif-

inversely with the severity of the disease, or of the particular case of the disease Variations in the dosage of the infecting pathogen and in the susceptibility of the host are important factors Local infections at the point of entry, such as diphtheritic and scarlet fever infections of the throat, usually have short incubation periods Although whooping cough is a local infection of the trachea, the production and absorption of toxin is probably necessary before the characteristic paroxysms are caused, hence the incubation period is slightly longer

The second stage is the *prodromal stage* or stage of invasion, which lasts from the onset of symptoms to the acme of the fever, or in the exanthemata until the appearance of the characteristic eruption.

The *fastigium* is the stage which lasts from the stage of invasion to the time when the temperature begins to fall and the exanthem to disappear

A stage of *defervescence* is sometimes described following the fastigium and lasting until the temperature has returned to normal

Then follows the stage of *convalescence* which lasts until the person has returned to normal health

Contagious diseases must be studied from the following definite viewpoints. (1) The focal manifestations, that is, the symptoms and signs due to the infection at its point of affinity (often the portal of entry), such as the pharynx in diphtheria and scarlet fever, the salivary glands in mumps, and the meninges in meningococcus meningitis (2) The systemic manifestations, that is, the symptoms and signs due to the generalized infection as in smallpox or measles, or to the toxemia which is the result of the circulation in the blood of the toxins produced by the invading organism (3) The symptoms and signs due to infection with a secondary organism, the primary organism having paved the way and facilitated infection with a secondary microbe.

Because there may be great variations in the virulence and dosage of the infecting viruses or bacteria and because

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This group of diseases includes smallpox and chickenpox, measles and rubella, scarlet fever and typhus fever. These diseases have in common an incubation period, prodromal symptoms, an exanthem and an enanthem (eruptions on the skin and mucous membranes respectively), and finally a desquamation, but typhus fever, while communicable only through the flea as intermediary, is therefore not contagious as are the others. The enanthem appears during the prodromal period and usually persists until the exanthem is fully out. It is of great diagnostic importance, particularly in measles and scarlet fever. The exanthem in each disease shows first as an erythema or congestion of the skin. This erythema ultimately becomes general in its distribution, but each disease has its selective area for first appearance. Measles, rubella, and smallpox usually show first on the face, chicken pox and scarlet fever on the trunk. With all of them the erythema spreads rapidly. The initial erythema may be macular or diffuse from the onset; when macular, it may rapidly become diffuse, or it may remain macular throughout its course. The coalescence of macules into diffuse areas may be general or in variously sized patches. The erythema varies both in intensity and duration in the dif-

ferent diseases, and also in different cases of the same disease

In general, the erythema is the initial or congestive period of an exudative inflammation. Among the exanthemata, enough exudate to be appreciable to the eye and finger is invariably present in chickenpox and in smallpox, usually present in scarlet fever, sometimes in measles, rarely in rubella The initial exudate in smallpox is purulent, in all the others it is serous In scarlet fever we have miliary, punctate vesicles, in measles and rubella, the vesicles, when present, which is infrequent, vary according to the size of those macules which go on to the exudative stage. In scarlet fever, measles, and rubella, the exudate is entirely absorbed and there is no scab formation. In smallpox and chickenpox the absorption is only partial so there is always scab formation.

Desquamation is the final stage of the eruption Any prolonged congestion of the skin causes an increase in the proliferation of epithelial cells. This is followed by an increase in the amount of deciduous epithelium in the form of a branny scurf, like dandruff The desquamation of measles and that of rubella are usually of this character, the former being the more marked. Usually in scarlet fever there is sufficient exudate to separate the outer layers of epithelium in patches or sheets of varying size and thickness, most noticeably on the palms and soles. The desquamation here is coarse and conspicuous

In smallpox and chickenpox the diagnostic value of desquamation is great. The presence of scabs and crusts with more or less peeling of skin about the lesions, together with their distribution, makes a diagnosis practicable late in the disease as well as early. With scarlet fever, measles, and rubella, the situation is quite different. Since there may be little or no exudate in a scarlet fever exanthem and on the other hand an unusual amount of exudate in either measles or rubella producing a coarse desquamation, it is evident that desquamation can at times be of little differential value It is necessary to have the corroboration of a history of exposure, or of other symptoms and signs, or of complica-

tions. Any inflammation of the skin, or prolonged congestion, due to whatever cause, is followed by some form of desquamation. So a differential diagnosis between these diseases, based on desquamation alone, is a difficult and hazardous procedure.

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2

Serum Reactions

In persons hypersensitized to a greater or less degree to certain foreign proteins, the administration of those proteins, as for example the proteins of horse serum, causes certain clinical reactions and phenomena which do not occur in persons not so sensitized. Since animal sera containing antitoxins are the specific remedies for several of the contagious diseases, especially diphtheria and tetanus, these diseases are frequently complicated by so-called serum reactions.

An antitoxin is a compound capable of counteracting the toxin of a particular microorganism. Various animals can be used for the manufacture of antitoxic sera but most antitoxins on the market are in horse serum. An unrefined serum contains at least four kinds of protein, albumin, and alpha, beta, and gamma globulins, which act as antigens and combine with the antibodies that are present or develop within or on individual cells in a patient's blood, thus causing the serum reactions. By a refining process which includes a selective digestion of the proteins of the antitoxic horse serum or plasma, up to 80 per cent of the coagulable protein is digested. The remaining portion of globulins, containing most of the antitoxic properties, is dissolved in freshly distilled water, and comprises the so-called refined concentrated antitoxins available today. Partly because of the resulting smaller bulk of the dose and partly because of the removal of the undesired proteins, the incidence of serum reactions is materially lessened.

THE ETIOLOGY OF SERUM REACTIONS

From the viewpoint of his reactivity to foreign proteins, man is of three general types:

1. Those naturally hypersensitive to a foreign protein, a condition called "atopy," and one dependent on an hereditary influence. Hay fever, allergic asthma, and infantile eczema are instances of comparatively moderate atopy, while the fortunately rare but terrific constitutional responses that may follow the ingestion of egg-white or the injection of horse serum, are instances of severe atopy, or marked hypersensitization. The inciting antigens in these cases are called "atopens" and the specific antibodies present in the blood cells "reagins," because they differ from ordinary antigens and antibodies in certain details

Sensitization in cases of this type may be very marked, at times to an almost unbelievable degree In fact, 1 minim of horse serum injected intravenously has in one instance caused death.[1]

The hereditary factor is not yet satisfactorily explained Inasmuch as extremely minute quantities of an antigen may sensitize, and since various antigens easily may enter the body as such, through the digestive and respiratory tracts and perhaps in other ways, it is possible that the rôle of the hereditary factor in certain forms of hypersensitiveness consists of the development in the tissues of special tendencies to respond to antigens, and hence that atopy, like anaphylaxis, is really due to sensitization

2 Those sensitized by the previous absorption or injection of an antigen such as a serum Anaphylaxis is a reaction of hypersensitiveness which occurs when an otherwise harmless protein is injected into such a being previously sensitized by an injection of the same protein. True generalized anaphylaxis occurs most typically in animals, where incidentally atopy never occurs, and such anaphylaxis differs

[1] Boughton J A M A, 73, 1912, 1919

from atopy in that besides being always artificially produced, it is temporary and never inherited [2]

There is always an incubation period to this state of sensitivity which takes seven to ten days to develop, is at a maximum a few weeks after the injection, and gradually diminishes thereafter, possibly even disappearing in the course of years Sensitization of this type is usually to a much less degree than with the former group Fatal accidents, however, have occurred in both groups but the majority of the deaths reported from serum accidents have been in atopic individuals as only a small percentage of those artificially sensitized attain a dangerous degree of sensitization In both groups the variation in the intensity of the sensitization covers a wide range. In certain individuals injections of the formerly widely used horse toxin-antitoxin, 1 cc of which contained a minute quantity (less than 0 0001 cc) of horse serum, was sufficient to increase their sensitivity to horse serum to a dangerous extent (See Fig 3, page 46) Moderate sensitizations from this source were quite common

Of three successive serum accident deaths at the Willard Parker Hospital, two (Nos. 1643–1931, and 2569–1932) were of patients sensitized by recent previous therapeutic injections of diphtheria antitoxin The third (No 367–1934) was of a child whose only previous injection had been of toxin-antitoxin three years before In all three children intracutaneous tests were negative, and in the latter two, ophthalmic tests also were negative Autopsies done only in the first and third cases confirmed the clinical diagnosis of anaphylactic deaths Probably none of the three patients was atopic, but all three had greatly accelerated reactions due to known previous injections. Incidentally there is no known test by which one can determine in advance whether a second injection of serum, given after the completion of a serum reaction

[2] The term "anaphylaxis" is in common usage, however, as a synonym for hypersensitiveness, and particularly for the extreme forms of specific hypersensitiveness that are evidenced by acute and violent manifestations Some purists restrict the term to the acquired hypersensitiveness of animals

due to a first injection, will or will not cause a dangerous reaction such as the three fatal ones mentioned

3. Normal or unsensitized individuals, in whom immediate serum reactions do not occur. They may, however, develop serum sickness even following a first injection of a serum Whereas the injection of a homologous serum (for instance that of human convalescent serum or gamma globulin into a measles patient) does not produce reactions except in very rare and unexplainable instances, the injection of a heterologous or foreign serum (such as horse antitoxin) provides an antigen to stimulate in the body cells the production of antibodies which when enough have accumulated, enter the circulation and combine with protein antigens from what survives of the foreign serum, to form toxic substances which may be responsible for the symptoms of serum sickness Thus the reaction may be delayed from six to twelve days or more until the antibodies are sufficiently numerous On the other hand, by this time the foreign serum may have been mostly eliminated, so there may be little or no reaction until after a later or second injection of the foreign serum When the antibodies are already present in number at the time of the injection, as from a previous injection or in atopic and anaphylactic patients, the reactions may be accelerated and aggravated or even may become immediate and severe

Perhaps 10 per cent of human beings are constitutionally insusceptible to serum reactions Negroes and the American Indians appear to be less susceptible than white people The serum from some horses is more apt to cause serum reactions than that from other horses, and fresh serum more than old serum.

Concentration of a serum, although preserving most of the antibody content despite the lowering of the serum-protein content, definitely lowers the incidence of serum sickness Likewise, in diphtheria, the chance of a serum reaction is apparently in inverse ratio to the severity of the attack Diphtheria toxin seems to counteract both the frequency and the severity of serum reactions In rare instances the

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between one and twenty-four hours, and after twenty-four hours respectively.

1. Anaphylactic Shock or Serum Accidents.—In markedly sensitized patients such as atopic individuals suffering from asthma due to horse dander, the injection of a horse serum, especially if given intravenously, may cause profound shock, collapse, and even death within two to ten minutes. Fortunately this reaction occurs very seldom, though probably more frequently than once in 70,000 injections, the figures usually given. Such a death may follow a first injection of serum, as in an atopic individual, or a second injection if the first was at least ten to fourteen days before and markedly sensitized the patient, thus exerting a highly accelerated reaction

The patient becomes restless and anxious, sometimes even while the injection is still being given. Breathing is labored and deep with sometimes a curious expiratory difficulty, asthmatic wheezes may be heard, and there may be a tight cough, cyanosis, nausea, and a cold, clammy sweat, also vomiting and involuntary defecation Angioneurotic edema of the face, tongue, or throat may be a conspicuous feature. Marked pallor and a rapid thready pulse develop, and the blood-pressure falls below a measurable point. The patient may go on into profound shock and coma, and unless immediate help is given death from respiratory failure may supervene within a very few minutes from the time of the injection Ophthalmic and intracutaneous tests will almost always identify the atopic individuals liable to have this type of reaction but will not accurately identify those highly sensitized by previous injections of serum.

Pathology.—Descriptions vary greatly of the findings at

ciently similar to suggest that the frequent cause of death is failure of the right side of the heart and inability to main-

intravenous injection of human serum has caused a serum reaction with chills and fever, the reason for which is not understood. Sensitization to human serum, and anaphylaxis following its administration are unknown. Ether anesthesia, despite the belief of some to the contrary, does not preclude the possibility of an anaphylactic reaction, should a serum be given during an operation

The route of administration of serum is of some importance. The routes in the order of increasing danger are subcutaneous, intramuscular, intraperitoneal, subdural, and intravenous; but even a subcutaneous injection of 0 5 ml. of serum has been reported fatal in a hypersensitive patient. Eight (0 37 per cent) of 2132 Schultz-Charlton intracutaneous injections of less than 0.02 ml each of horse serum at the Willard Parker Hospital were followed by serum reactions of mild degree. In general, the larger the dose of serum proteins, the more likely and severe is the reaction.

Statistics as to the incidence of serum reactions vary greatly, differing as to the preparations of serum used. Unrefined and unconcentrated sera may give reactions of varying degree in 30 to 50 per cent of cases but refined preparations sometimes cause reactions in less than 10 per cent even when given in therapeutic dosage

Toxoids and bacterial vaccines can occasionally cause allergic reactions similar to those caused by heterologous serums Severe reactions are rare, however, especially in children.

THE CLINICAL MANIFESTATIONS OF SERUM REACTIONS

For the purpose of description, serum reactions may be divided into three main types as follows, although borderline reactions between the types are observed as commonly as are the main types themselves Some writers prefer the classification of *immediate, accelerated,* and *late serum reactions,* the approximate time limits being up to one hour,

One-half to three hours following the administration of an antitoxin, particularly when it has been given intravenously, there may be a severe chill, with very high fever, reaching even 107° F. or more, and with very great distress. There may be vomiting, joint pains, more or less general edema and occasionally an erythema. The fever usually subsides rapidly and all other symptoms clear up within a few hours, particularly if the patient is given epinephrin and possibly morphine and atropine. Curiously enough, when such a reaction occurs, the disease for which the serum was given, such as diphtheria, is occasionally cured much more rapidly than are cases of the same disease in which this reaction is not obtained. The temperature may drop to normal within twelve hours of the onset of the chill and remain there for the rest of the convalescence. The membrane also is apt to clear up much more rapidly.

3. **Serum Rash or Serum Sickness or Serum Disease.** This is the commonest type of reaction to antitoxin and is unpredictable because the preliminary skin test is negative. The incubation period is usually from five to eight days but longer periods are not uncommon. On the other hand the time of incubation is shortened with *repeated* administrations and is eventually reduced to a few hours or even minutes, the intensity of the clinical symptoms being often correspondingly increased. The term "*Accelerated reactions*" is applied to these instances of comparatively rapid onset.

A case of serum disease is apt to run from two to four days, with the more severe reactions lasting even longer. The most marked general feature is the skin reaction or eruption. This is quite variable in its character. Occasionally there is only a general erythema or congestion of the skin, or there may be a pure urticaria, or eruption of hives, resembling white welts of irregular size and outline. A combination of erythema and urticaria is much more usual. A serum eruption may also at times be macular in appearance and suggestive of the exanthem of measles or in rare instances it may take the form of erythema multiforme or even purpura. The

tain pressure in the pulmonary system as a result of spasm of the pulmonary arterioles. There is a resulting pulmonary emphysema, dilation of the right side of the heart, and evidence of general venous stasis In other cases there is a

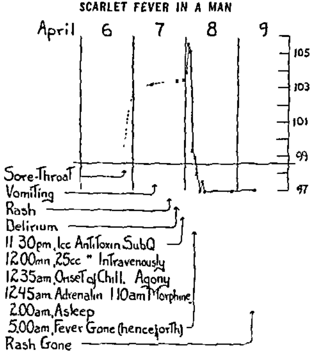


FIG 2 —An illustration both of a severe protein-shock reaction, and of the resulting benefit obtained from the use of unrefined scarlatinal antitoxin in an exceedingly toxic case of scarlet fever in a man. (Courtesy of the Archives of Pediatrics)

general congestion of the splanchnic area with multiple hemorrhagic foci as in the adrenals and kidneys.

2. **The Thermal Reaction, or Protein Shock Reactions.**— This reaction is probably not a result of sensitization but a shock reaction due to the injection of a foreign protein.

A leukopenia is generally present during an attack of serum sickness unless there is some infection present to counteract it, and there may be a mild eosinophilia as the rash clears up. The serum of a patient with serum sickness contains an agglutinin against sheep erythrocytes, but this antibody is different from the heterophile antibody of infec-



FIG. 4.—Arthus phenomenon in right buttock of twelve-year old girl. Day 1. 10,000 units diphtheria antitoxin injected deep in right buttock. Day 5. 10,000 units diphtheria antitoxin injected deep in right buttock. Day 6. 15,000 units diphtheria antitoxin injected deep in right buttock. Day 7. High fever. Swelling of right buttock with extensive dark discoloration and beginning bleb formation. Day 8. Extensive early gangrene. Photograph taken. Most of buttock and thigh eventually sloughed away. (From the collection of Jerome L. Kohn.)

tious mononucleosis. The red cell agglutinin of serum sickness is adsorbed by guinea pig kidney and by boiled beef erythrocytes, that of infectious mononucleosis by guinea pig kidney only.

Serum sickness may be followed four to ten days after the first wave by a mild relapse with recurrence of the urticaria and possibly other manifestations. The local reaction to an intramuscular injection is apt to be characterized by redness,

itching due to the urticaria is usually most distressing and is not relieved permanently until the eruption clears up after two to five days. This type of serum reaction may be unaccompanied by fever, but in the majority of cases some elevation of temperature is present, and occasionally the record shows daily heights of 104° F. for several days, beginning a day or two before the other manifestations of the reaction

SERUM SICKNESS

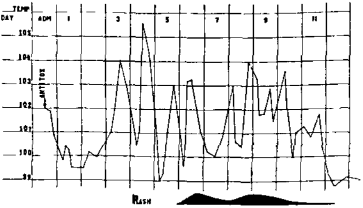


FIG 3 —Showing an unusually severe case of serum sickness with nine days of fever, occurring in a boy, aged three years, recovering from a pseudo-diphtheritic laryngitis One year before he had received three injections of horse toxin-antitoxin, but a follow-up Schick test had not been made

Joint pains are not uncommon, there is often considerable malaise, and a general slight lymphadenitis may occur, involving particularly the nodes nearest to the site of the injection. There is frequently found a certain amount of edema, as of the face, and there may also be vomiting and evidences of temporary kidney involvement such as albuminuria and *oliguria* *Rarely, cardiac injury occurs in serum* sickness, both myocarditis and pericarditis having been reported.

authorities prefer 1 to 100). This test is positive if at the end of twenty minutes the wheal of the injection has enlarged and an area of redness at least 1 cm in character has formed around it, and particularly if projections like pseudopods have appeared from the wheal extending out into the surrounding area of erythema. Undiluted serum may cause in non-sensitive individuals, a reddening of the skin at the site of injection. In patients known to be hypersensitive it is safer to do a simple scratch test before doing the intracutaneous test.

The other is the conjunctival test which should especially be done if the skin test is positive. This consists of instilling 1 drop of a 1 to 10 dilution of serum inside the lower eyelid of the patient. The occurrence of congestion, swelling and discomfort indicates a positive test. This reaction is easily counteracted by instilling 1 or 2 drops of a 1 to 1000 solution of epinephrine inside the lower eyelid, a procedure which should be followed in all such reactions. Otherwise the inflammation, if allowed to persist, may cause corneal ulceration in isolated cases. Ophthalmic tests are less sensitive than intracutaneous tests but probably more reliable as an index of susceptibility to serum reactions.

The results of the intradermal and ophthalmic tests should be interpreted as follows: (1) If the ophthalmic test is negative and if there is no more than a moderate area of simple redness at the site of the skin test, then antitoxin may be given by any route. Despite negative tests, it is a good practice to give 1 ml of the serum subcutaneously one-half to one hour before making a larger injection of antitoxin intravenously. (2) A definite wheal-like reaction of 2 or more centimeters with surrounding erythema indicates skin sensitivity, but not necessarily systemic sensitivity. However, if the ophthalmic test is negative, the dose of antitoxin can probably be safely given, although a local or general serum rash may rapidly develop. One-tenth of 1 ml of the serum should be given subcutaneously, and if there is no untoward effect in ten or twenty minutes, 1 ml should be

pain and swelling for two or three days, and the eruption of the general serum reaction may appear locally around the site of an intramuscular injection before the local inflammation due to the actual injection itself has subsided.

During the course of serum disease, if a further injection of serum is made, as for a blanching test, focal necrosis may occur. However, this is less likely to occur if daily injections of serum are given as for tetanus, than if the serum sickness is due to a single previous injection several days before. Instances have been reported of intramuscular injections made in the presence of a reaction due to a previous injection, though not necessarily in the same site, being followed by focal skin gangrene and subjacent sterile necrosis involving a considerable area. (See Fig. 4.) This may be the human counterpart of the Arthus phenomenon in animals, and is apparently due to a local tissue hypersensitivity (Gatewood and Baldridge) but a circulating toxin from an infection elsewhere may perhaps have to be present also. The actual pathology of the Arthus phenomenon apparently is an arteritis and a periarteritis These blood vessel lesions lead to intravascular thrombi with resulting necrosis

PROPHYLAXIS IN SERUM REACTIONS

To avoid the likelihood of serious serum reactions, before the administration of a serum all adults and older children should be questioned for possible indications of sensitization, such as a history of asthma, hay fever, angioneurotic edema and previous injections of antitoxin. Except in emergencies, tests to determine sensitization should be done before any injection of antitoxin. A patient's reaction to tests on a previous occasion or his reaction to a previous injection of serum will of course not indicate his probable reaction to a proposed injection.

Two tests are available, and it is usually desirable to use both. One is the intracutaneous injection of 0 1 ml. of a solution of antitoxin *diluted 1 to 10 in sterile saline (some*

authorities prefer 1 to 100) This test is positive if at the end of twenty minutes the wheal of the injection has enlarged and an area of redness at least 1 cm in character has formed around it, and particularly if projections like pseudopods have appeared from the wheal extending out into the surrounding area of erythema Undiluted serum may cause in non-sensitive individuals, a reddening of the skin at the site of injection In patients known to be hypersensitive it is safer to do a simple scratch test before doing the intracutaneous test

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The results of the intradermal and ophthalmic tests should be interpreted as follows. (1) If the ophthalmic test is negative and if there is *no more* than a moderate area of simple redness at the site of the skin test then antitoxin may be given by any route Despite negative tests it is good practice to give 1 ml of the serum subcutaneously one-half to one hour *before making a larger injection* of antitoxin intravenously (2) A definite wheal-like reaction of 2 or more centimeters with surrounding erythema indicates skin sensitivity, but *not necessarily systemic sensitivity*. However, if the ophthalmic test is negative, the dose of antitoxin can probably be safely given, although a local or general serum rash may rapidly develop One-tenth of 1 ml of the serum should be given *subcutaneously*, and if there is no untoward effect in ten or twenty *minutes*, 1 ml should be

similarly given. If ten minutes later there is still no notable effect, the full dose may be given intramuscularly or intraspinally if indicated, but the intravenous route should be avoided unless it is absolutely necessary for the life of the patient (3) A positive ophthalmic reaction, with or without a positive intradermal test, indicates a probable systemic reaction Here the degree of caution is proportional to the degree of reaction obtained, and if serum from a different species of animal is not available (such as bovine diphtheria antitoxin), attempts must be made to hyposensitize the patient, that is, to diminish sensitization enough to permit the injection of the desired amount of serum.

It must be remembered that there is a distinction between local or tissue hypersensitivity and general or constitutional hypersensitivity, and serious reactions have been reported in people giving negative skin tests (See page 40) Accordingly in the intravenous administration of any serum, proper precautions should always be observed, these are (*a*) a warmed but not overheated and coagulated serum, (*b*) a very slow injection, (*c*) careful observation of the patient, (*d*) hypodermic preparations of epinephrine and possibly atropine instantly available and (*e*) a tourniquet ready for application above the site of injection

There is no known method of assuring the prevention of serum sickness, the delayed type of serum reaction, but the incidence can be diminished by refining the serum The injudicious use of prophylactic doses of serum is to be guarded against When essential, prophylaxis might well be done with human, rabbit, or bovine serum if available

In consideration of the patient's comfort large amounts of serum when to be given intramuscularly, are best injected in the buttocks. Although sometimes advocated, the lateral aspects of the thigh are to be avoided because of the added
[illegible] a.
[illegible] *ry to give horse*
[illegible] those who give a
history of asthma or other possible sensitization especially if

to horses, the first injection of serum should be subcutaneous and in an extremity, and should be not more than 0.01 ml of serum. A tourniquet should be in place above the site of injection ready to be tightened at the first sign of a serum reaction. It may be thought wise in extreme cases to use for this first injection serum diluted 1 to 100 in saline. A preliminary injection in another extremity of 3 to 6 minims of epinephrine before or with an injection of serum will usually prevent the occurrence of a possible anaphylactic shock but it does not prevent the subsequent development of serum sickness. If no unfavorable symptoms occur, the dose may be doubled every thirty minutes until 1 ml. of serum has been given subcutaneously; then thirty minutes later 0.1 ml of serum diluted in saline may be given intravenously. At intervals of twenty minutes thereafter, the intravenous dose may be doubled until the required amount of serum has been given. In cases where it is necessary to inject the serum intraspinally, the same procedure should be followed until a dose of perhaps 10 ml has been tolerated intravenously, then that amount may be given with caution intraspinally. In patients not highly sensitized, particularly those whose sensitization has resulted from a previous serum treatment, this procedure may be materially shortened if no unfavorable symptoms have occurred after the early doses. The first intravenous dose in sensitive individuals should not be more than one-tenth of the last subcutaneous or intramuscular dose. The serum should always be warmed to body temperature before being injected either intravenously or subdurally, and epinephrine for hypodermic injection should of course be always instantly available. The state of hyposensitiveness usually lasts a few days. In very rare instances it may be impossible to reduce the sensitization of an "atopic" individual.

On the other hand if anaphylactic reaction does occur and is readily controlled by appropriate treatment, the patient at once enters a refractory stage for some hours and can be given further injections of the same serum with reasonable

safety, thus enabling the completion of a full therapeutic dose of the antitoxin.

To avoid local necrotic reactions due to a local or tissue hypersensitivity (the Arthus phenomenon), serum should not be injected in the general vicinity of a recent subcutaneous or intramuscular injection nor, if possible, anywhere in the presence of a serum reaction.

SUMMARY: The intravenous administration of a foreign serum:

1. Inquire about the possibility of hypersensitivity
2. Do sensitization tests.
3. Have a tourniquet and epinephrine quickly available.
4. If tests are negative, inject a small quantity of serum subcutaneously and wait twenty minutes.
5. Inject the rest of the serum at body temperature and very slowly.
6. Watch constantly for any indications of a reaction.

THE TREATMENT OF SERUM REACTIONS

In case of anaphylactic shock, rapid work is necessary to save the life of the patient. A tourniquet should at once be tightened above the site of the injection to prevent temporarily the continued absorption of the serum, and cold applications on the site of the injection may further the same object. Five to 15 minims of a 1 to 1000 solution of epinephrine hydrochloride should be given at once by hypodermic in the opposite extremity. This drug acts to overcome the bronchospasm and constriction due to the serum reaction. If given intravenously, the epinephrine must be very freely diluted. *The body should be warmed with hot blankets or by the*

For the protein-shock reactions, epinephrine in large doses and morphine and atropine have been customarily used, apparently with great benefit. If, however, the blood pres-

sure is increased markedly with the chill, as has been found to be usually the case, inhalations of amyl nitrite may prove notably beneficial. Temperatures of over 106° F. should be actively and immediately combated by sponging with cold water or by application of cold packs.

For the serum disease, hypodermic injections of an aqueous solution of epinephrine hydrochloride being prompt relief to the itching and general distress, and massaging the site of the injection may prolong its effect. Since in marked cases this relief is apt to last only an hour or two it is advisable to limit the use of the drug to those times when the patient especially needs relief, such as at bedtime and before a nap. A 1:1,000 suspension of epinephrine in sesame oil, which is slowly absorbed may provide a more prolonged effect. It is given by intramuscular injection every six hours, in dosage varying from 0.2 ml. for infants to 1.0 ml. for adults. Ephedrine sulphate, 16 mgm. every three or four hours for a six-year-old child, may lessen the need for the epinephrine injections.

Antihistamine drugs are sometimes very effective in serum sickness, while in other instances they seem to be of little benefit. In every case, however, they should be given a trial. The mode of action of these drugs is not clearly understood, but it may be connected with their ability to inhibit the enzyme monoaminoaminase which breaks down adrenalin (the antagonist of histamine). While there are a great number of antihistaminic drugs on the market, our experience has been limited to the use of only two in serum sickness. These are Benadryl* (tripelennamine hydrochloride) and Pyribenzamine* (diphenhydramine hydrochloride), which are given by mouth in a daily dose of 4 to 8 mgm. per kilogram of body weight, (total daily dose of 200 mgm. should not be exceeded).

Adrenocortical hormone (ACTH) of the anterior pituitary and cortisone (and related adrenal steroids) are frequently of great benefit in relieving the symptoms of serum sickness. The action of the adrenal steroid hormones may be due to the fact that they diminish the intensity of the response of

safety, thus enabling the completion of a full therapeutic dose of the antitoxin.

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tissues to harmful stimuli The effect of ACTH is due to its stimulation of the adrenal gland to secrete its steroid hormones The dose of cortisone (compound E) is from 10 to 60 mgm by mouth, every five hours, depending upon the weight of the patient. Meticorten® (prednisone) may also be employed, in approximately ¼ or ⅕ of this dosage. ACTH must be given by parenteral injection to be effective. The *dose recommended for serum sickness is 10 to 25 units every* six hours, by intramuscular injection.

In some patients liberal doses of bromides give relief from the very real suffering due to the itching. General baths in soda and water, or bran baths, may mitigate the itching, and local application of calamine and zinc lotion is also helpful Where the itching is not very severe, it may be sufficient to dust the skin with a talcum powder to 50 grams of which 0 25 gram of menthol and 5 ml of alcohol have been added Aspirin in large doses may be necessary for relief of joint pain as well as for the headache. The temporary kidney insufficiencies should be treated with careful regulation of fluid intake and of salt

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cycline itself. Three other antibiotics—polymyxin, bacitracin and neomycin are also useful under proper circumstances, but their greater toxicity sharply limits their usefulness

MODE OF ACTION OF ANTIBIOTICS

Some antibiotics are bactericidal at concentrations obtainable in body fluids, while others are bacteriostatic only In the bactericidal category are penicillin, streptomycin, erythromycin, polymyxin, neomycin and bacitracin. Sulfonamides, the tetracycline compounds (aureomycin, terramycin and tetracycline) and chloromycetin are bacteriostatic

In general, antibiotics affect bacteria by interfering in one or more ways with the metabolism of the susceptible organism. Penicillin acts upon bacteria by halting the action of the bacterial enzyme system which transports glutamic acid into the cell. Thus, the bacteria are deprived of an essential metabolite. Penicillin also decreases the rate of conversion of amino acids into protein within the bacterial body, and in addition, it inhibits synthesis of ribose nucleic acid, a nuclear compound of particular importance in the metabolism of Gram-positive organisms These actions cause suppression of growth and multiplication, and bring about death of the bacterial cells

The adverse effect of streptomycin upon susceptible bacteria is explained in part by its inhibition of the oxidation of pyruvate and oxalacetate which are essential for basic energy exchange of the cell The tetracycline drugs cause derangement of the phosphorylating mechanism, thus preventing the incorporation of phosphorus into nucleic acid and into organic phosphates Chloromycetin probably acts as an antimetabolite for the amino acid phenylalanine which it closely resembles structurally In this way it inactivates enzymes necessary for protein synthesis. Chloromycetin also affects some organisms (*E coli*) by inhibiting formation of the enzyme gluconkinase which converts gluconate into 6-phosphogluconate.

3

The Antibiotics and the Sulfonamides

THE introduction of the sulfonamide drugs for human use in 1933 and the development of penicillin in 1941 have brought about a remarkable advance in the control of infectious diseases The reduction of the death rate from pneumonia, and the greatly reduced incidence of empyema are examples of this effect Streptococcal infections including scarlet fever have to a very great extent come under control, and it is quite likely that the incidence of rheumatic fever and of nephritis has been consequently reduced Otitis media has lost much of its danger and mastoiditis has become a very rare complication The case fatality rate from meningococcic meningitis has been reduced in a very striking manner, in fact survival and complete recovery rates in all types of bacterial meningitis have improved greatly Antibiotics effective against rickettsial diseases are available and these agents are also effective against the organisms of the lymphogranuloma-ornithosis group No antibiotics effective against true viruses have been discovered, but antibiotics effectively prevent and cure the bacterial infections which complicate viral diseases. For example, in the treatment of measles, this effect of antibiotics upon secondary bacterial invaders has been of the utmost importance.

Over three hundred antibiotics have been isolated and identified but most are too toxic to be of practical value. Only seven antibiotics are in common use today—penicillin, streptomycin, chloromycetin, erythromycin and the three tetracycline compounds—aureomycin, terramycin and tetra-

cycline itself. Three other antibiotics—polymyxin, bacitracin and neomycin are also useful under proper circumstances but their greater toxicity sharply limits their usefulness.

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Sulfonamides interfere with the formation of folic acid, a substance necessary for the growth of many bacteria. Sulfonamides structurally are very similar to para-aminobenzoic acid which is contained in the folic acid molecule. Because of this similarity they compete with para-aminobenzoic acid for incorporation into folic acid The resultant complex containing the sulfonamide radical is inactive Because it has usurped the site normally used for the incorporation of para-aminobenzoic acid, folic acid is not formed and bacterial growth is suppressed. Thus this action of the sulfonamide is merely bacteriostatic—the infected animal must complete the process by destroying the organism by phagocytosis or other means.

RESISTANCE TO ANTIBIOTICS

Bacteria are resistant to antibiotics or may become resistant to them in several ways, which include the following:

1 They may produce substances which neutralize the action of the antibiotic This type of resistance has been termed natural resistance It is characteristic of many strains of staphylococci which are resistant to penicillin because they produce penicillinase — an enzyme which inactivates the antibiotic

2. In a bacterial population causing an infection, individual *cells arise by spontaneous mutation which are resistant* to the antibiotic which is being used The resistant cells multiply freely and soon make up the entire bacterial population This mechanism is involved in the emergence of strains resistant to streptomycin and the resistant strains may even become dependent upon streptomycin as a growth factor. The mutants resistant to streptomycin are stable and tend to preserve their resistant character. This phenomenon has greatly reduced the usefulness of streptomycin in the treatment of many infections in which it was originally very effective.

Streptomycin is the antibiotic most affected by the emergence of resistance strains, other antibiotics have suffered a much less striking loss of value. Nevertheless, all antibiotics in common use have lost some of their effectiveness against bacteria which at first were most sensitive There is reason to believe that each new antibiotic will be subject to a loss of potency to a greater or lesser extent. An example of this tendency has been furnished by Lepper and his associates These authors showed that the proportion of erythromycin-resistant staphylococci isolated from the personnel of a hospital rose progressively from zero to 75 per cent during the five months following the introduction of erythromycin as a therapeutic agent into the hospital

The present day ineffectiveness of penicillin against staphylococci is well known, and will be referred to later Fortunately there has been no significant emergence of penicillin resistant strains of Beta hemolytic streptococci, pneumococci, gonococci, or Treponema pallidum

COMBINATIONS OF ANTIBIOTICS AND POSSIBLE SYNERGISM

For the great majority of infections, only one antibiotic should be employed However, for the treatment of certain infections and in special circumstances, it may be advisable to use antibiotics in combination Theoretical considerations favoring such use of antibiotics include the following

1. Effectiveness may be increased by providing more than one method of interference with bacterial metabolism.

2. Combinations of antibiotics may prevent, depress or delay the emergence of resistant organisms An example of this phenomenon is the effect of a combination of erythromycin and penicillin in delaying the appearance of resistance of staphylococci Another example is the effect of the combination of para-amino salicylic acid and streptomycin in retarding development of resistance of Mycobacterium tuberculosis to the latter drug.

3. Additive and synergistic effects have been demonstrated by *in vitro* and *in vivo* tests in the laboratory.

4. Clinical experience has demonstrated the greater effectiveness of certain combinations of drugs over a single antibiotic. Examples include the superior effectiveness of:

   (*a*) Penicillin and sulfonamides in pneumococcic and streptococcic meningitis

   (*b*) Penicillin and sulfonamides in actinomycosis.

   (*c*) Penicillin and streptomycin in subacute bacterial endocarditis

   (*d*) Streptomycin and para-amino salicylic acid in tuberculosis

   (*e*) Streptomycin and aureomycin (chlortetracycline) in brucellosis

On the other hand, antagonism or interference between antibiotics has been demonstrated in the laboratory by *in vitro* and *in vivo* experiments. However, these experiments have demonstrated antagonism only under restricted conditions and their practical significance is probably not very great. Clinical experience in general attests the value of combined antibiotic therapy when it is properly employed, as indicated above. For practical purposes it seems clear that *the physician may use antibiotics in combination when they are needed with little fear of encountering antagonism*.

CHANGE IN BACTERIAL FLORA AND SUPERINFECTION

When an antibiotic is administered, changes in the bacterial flora of the respiratory passages, intestinal tract and of the skin occur. Organisms susceptible to the antibiotic are eliminated or their growth is greatly reduced. Their restraining check upon non-sensitive organisms is thereby reduced, and these grow and replace the organisms injured by the antibiotic action. In most cases the new bacterial population causes no symptoms, because they are non-pathogenic or because the patient is immune to them. However, in some instances one or more of the newly dom-

inant species invades the tissues and causes infection In this way, Escherichia coli, Bacillus proteus, and Pseudomonas æruginosa and Monilia have become an increasingly difficult problem. This is particularly the case when some underlying systemic disease, such as cystic fibrosis of the pancreas, requires frequent or prolonged use of antibiotics

Toxicity and Hypersensitivity

In common with all drugs, the antibiotics in general use may produce undesirable effects upon the patient Great variation in individual tolerance is encountered both in type and severity of reaction Some of these are due to direct, toxic or irritating action of the drug on various tissues, while others result from allergy or hypersensitivity to the drug Toxic reactions may be due to the use of an excessive quantity of antibiotic, but some of these drugs are inherently toxic even in small dosage

TABLE 2

Reactions Due to Sensitization	*Toxic and Irritative Reactions*
1 Fever	1 Diarrhea
2 Eruptions—morbilliform	2 Nausea, vomiting
urticarial	3 Inflammation pain at site of injection
bullous	
purpuric	4 Albuminuria, hematuria, cylindruria
exfoliative	
contact dermatitis	5 Depression of renal function
3 Eosinophilia	6 Glossitis and stomatitis
4 Angioneurotic edema	7 Venous thrombosis
5 Glossitis stomatitis cheilosis	8 Hepatitis
6 Joint pain and swelling	9 Peripheral neuritis
7 Erythema multiforme	
8 Asthma	
9 Arthus reaction	
10 Anaphylactoid reactions	
11 Polyarteritis nodosa	
12 Disseminated lupus erythematosus	

As to reactions due to hypersensitization, these may follow the use of practically all antibiotics They usually occur ten to twelve days after treatment Sometimes they occur

TABLE 1.—SUSCEPTIBILITY OF PATHOGENIC ORGANISMS TO ANTIMICROBIAL AGENTS[1,2]

	PEN	*SM DHSM*	*CLTC*	*OTC*	*TC*	*CLA*	*BAC*	*PMB*	*SULF*	*ERY CARB*
Strep. hemolyticus	A	C(V)	B	B	B	B	B	O	B	B
Strep. viridans	A	C(V)	B	B	B	B	B	O	C	B
Strep. faecalis	A(V)	C(V)	B	B	B	B	B	O	C	B
M. pyogenes (Staph.)	A(V)	C(V)	B	B	B	B	B	C	B(V)	B
Diplococcus pneumoniæ	A	C(V)	B	B	B	B	B	O	B	B
Clostridium (tetanus, gas gangrene)	A(*)	O	C	C	C	C	C	O	C	B(V)
Corynebacterium diphtheriæ	A(*)	O	B	B?	B?	B	B	O	O	B
Bacillus anthracis	A(*)	B	B	?	?	B	C	O	B	?
Bacillus subtilis	A	B	B	B	B	B	B	O	B	B?
Neisseria gonorrhoeæ	A	C	B	B	B	B	B?	O	B	B
Neisseria meningitidis	A	O	B	B	B	B	B?	O	A	B
Hemophilus influenzæ	C	A	B	B	B	B	C?	B	B	B
Hemophilus pertussis	O	B	B	B	B	B	?	B	B	B
Hemophilus ducreyi	B	B	B	B	B	B	?	?	A	?
Klebsiella pneumoniæ	O	A	B	B	B	B	O	B	B	O
Erysipelothrix rhusiopathiæ	A	C	?	?	?	?	?	O	?	?
Escherichia coli	O	A	B	B	B	B	O	O	B	O
Aerobacter aerogenes	O	A(V)	B	B	B	B	O	B	B	O
Proteus vulgaris	O	A(V)	B(V)	B(V)	B(V)	B(V)	O	O	B	O
Pseudomonas æruginosa	O	C(V)	C(V)	C(V)	C(V)	C(V)	O	B	C	O
Salmonella typhosa	O	B	B	B	B	A	O	B	C	O
Salmonella spp. (paratyphoid, etc.)	O	B	B	A	A	B	O	C	C	O
Shigella spp. (dysentery)	O	B	B	B	B	B	O	B	A	O
Pasteurella pestis	O	A	B	B	B	B	O	B	A	O
Pasteurella tularensis	O	A	B	B	B	B	O	?	B	O
Brucella spp.	O	B	A	A	A	A	?	B	C	?

Streptobacillus moniliformis	A	*	?	?	*	?	*	?	*	?
Actinomyces bovis	A	O	C	?	*	*	A	?	B	*
Alcaligenes spp	*	C	B	*	*	C	O	*	*	*
Treponema pallidum	A	C	B	B	B	B	B	*	O	?
Treponema pertenue	A	C	B	B	B	B	?	*	O	?
Borrelia recurrentis	A	O	C	C	C	C	O	*	O	?
Spirillum minus	B	B	A	A	A	C	*	?	O	?
Leptospira icterohemorrhagiae	B	C	A*	B	B	B	?	*	O	?
Vincent's organisms	A	O	B	B	B	B	*	?	?	?
Mycobacterium tuberculosis	O	A	C	C	C	C	?	C	B(S)	O
Mycobacterium leprae	O	B	?	?	?	*	*	O	A(S)	?
Psittacosis virus	C	*	A	A	A	B	?	O	C	B
Lymphopathia venereum virus	C	O	A	A	A	B	?	O	B	B
Donovan body	O	B	A	A	A	B	O	*	O	B*
Trachoma virus	B	O	B	B	B	B	*	*	B	
Rickettsia spp	O	O	A	A	A	A	O	O	O	B
Vibrio comma	O	C	B(V)	B(V)	B(V)	C	O	O	B(V)	*

A—Drug of choice
B—Active, alternative
C—Weakly active
O—No significant activity
(V)—Significant variation in strain susceptibility
?—Insufficient data
(*)—Plus other specific therapy

PEN—Penicillin
SM—Streptomycin
DHSM—Dihydrostreptomycin
CLTC—Chlortetracycline
OTC—Oxytetracycline
TC—Tetracycline
CARB—Carbomycin
CLA—Chloramphenicol
BAC—Bacitracin
PMB—Polymyxin B
SULF—Sulfonamide
(S)—Sulfone
ERY—Erythromycin

A Penicillin—drug of choice—in an estimated 72% of bacterial infections encountered in temperate climates in a year (Krantz, J C, Jr Paper read before Annual Session of Medical Society of Pennsylvania October 20, 1954)

Adapted from 1 Welch, H, and others Principles and Practice of Antibiotic Therapy New York Medical Encyclopedia Inc 1954 2 Morgan, H J, and Branscomb B V Medicine of the Year 1953, Philadelphia J B Lippincott Company, pp 34 41 courtesy of Wyeth Laboratories

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Strep. faecalis	A(V)	C(V)	B	B	B	B	B	O	C	B
M. pyogenes (Staph.)	A(V)	C(V)	B	B	B	B	B	C	B(V)	B
Diplococcus pneumoniae	A	C(V)	B	B	B	B	B	O	B	B
Clostridium (tetanus, gas gangrene)	A(*)	O	C	C	C	C	C	O	C	B(V)
Corynebacterium diphtheriae	A(*)	O	B	B?	B?	B	B	O	O	B
Bacillus anthracis	A(*)	B	B	?	?	B	C	O	B	?
Bacillus subtilis	A	B	B	B	B	B	B	O	B	B?
Neisseria gonorrhoeae	A	C	B	B	B	B	B?	O	B	B
Neisseria meningitidis	A	O	B	B	B	B	B?	O	A	B
Hemophilus influenzae	C	A	B	B	B	B	C?	B	B	B
Hemophilus pertussis	O	B	B	B	B	B	?	B	B	B
Hemophilus ducreyi	B	B	B	B	B	B	?	?	A	?
Klebsiella pneumoniae	O	A	B	B	B	B	O	B	B	O
Erysipelothrix rhusiopathiae	A	C	?	?	?	?	?	O	?	?
Escherichia coli	O	A	B	B	B	B	O	O	B	O
Aerobacter aerogenes	O	A(V)	B	B	B	B	O	B	B	O
Proteus vulgaris	O	A(V)	B(V)	B(V)	B(V)	B(V)	O	O	B	O
Pseudomonas aeruginosa	O	C(V)	C(V)	C(V)	C(V)	C(V)	O	B	C	O
Salmonella typhosa	O	B	B	B	B	A	O	B	C	O
Salmonella spp. (paratyphoid, etc.)	O	B	B	A	A	B	O	C	C	O
Shigella spp. (dysentery)	O	B	B	B	B	B	O	B	A	O
Pasteurella pestis	O	A	B	B	B	B	O	B	B	O
Pasteurella tularensis	O	A	B	B	B	B	O	?	O	O
Brucella spp.	O	B	A	A	A	A	?	B	C	?

lactic reactions and 3 deaths have been reported with an iodinated penicillin preparation. Penicillin should not be administered to a person who has had a reaction to a previous dose of penicillin unless he is suffering from a severe infection for which no other antibiotic is effective. Persons suffering from hay fever or asthma should also be placed in the same category. Iodinated salts of penicillin should be avoided for all patients. There has been no clear-cut evidence of fatal anaphylaxis caused by the tetracycline drugs or by chloromycetin, bacitracin, neomycin or erythromycin.

USE OF ANTIBIOTICS

The antibiotics now available are effective against bacteria, Rickettsiae and the organisms of the psittacosis-lymphogranuloma group. No clear-cut evidence of their effectiveness against uncomplicated viral infections has been brought forward. In the general treatment of virus infections their role is limited to the prevention and treatment of secondary bacterial invasion in severe viral diseases such as measles. The widespread use of antibiotics for treatment of common colds and acute non-streptococcal pharyngitis has been criticized by many authors. It is believed by some authorities that this practice has caused unnecessary sensitization of many persons to antibiotics and that it has contributed to the emergence of resistant strains of organisms which were originally sensitive. While there is considerable justification for this point of view, it must be admitted that on clinical grounds it is most difficult to differentiate between streptococcal and non-streptococcal pharyngitis. Early treatment of respiratory infections which do not appear serious may be in part responsible for the great reduction in the incidence of serious complications and in the death rate following infectious diseases, which has occurred during the past fifteen years.

Under certain circumstances the decision concerning the [illegible]ion of an antibiotic presents no difficulty. This

promptly after the administration of a drug which the patient has never before received, this is most often encountered with penicillin Usually the allergic manifestations disappear when the antibiotic is eliminated, but they may persist for several weeks after cessation of treatment In some cases the reaction is very mild and may even disappear despite continuation of therapy, but in other instances the reaction is severe, and may be fatal Once a patient has shown evidences of hypersensitivity to an antibiotic, the drug should be forbidden for future use unless the risk of withholding it would be extremely serious, and no effective substitute is known

All antibiotics given orally may produce nausea, vomiting and diarrhea. These symptoms are probably most common with the tetracycline drugs, occurring in 10 to 30 per cent of patients They may also occur with chloromycetin, and large doses of penicillin given orally may produce the same effect Fever and eruptions of almost every description have been caused by all the antibiotics in use, but they are more common with penicillin and with sulfonamides It is estimated that 5 to 10 per cent of adults now react to penicillin in some unfavorable way The percentage of children showing adverse effects from penicillin is generally believed to be smaller In general, however, *antibiotic drugs are less likely to cause sensitization when administered by mouth than when given by parenteral injection*

The toxic effect of streptomycin upon the vestibular portion of the eighth cranial nerve and that of dihydrostreptomycin upon the auditory portion interfere seriously with the use of these drugs. Also, as mentioned earlier in this chapter, the nephrotoxicity of neomycin, polymyxin and bacitracin sharply limit their usefulness

Anaphylactic shock and death have been reported to have been caused by penicillin on a number of occasions Long in 1953, found records of 9 fatal reactions to penicillin in the literature. Seven of these patients had received penicillin previously, and 4 were asthmatic Fourteen severe anaphy-

Erythromycin (Erythrocin®) (Ilotycin®)	20 30 mg lb daily 4 × daily		10 mg lb per day 0 5 1 mg ml				5 mg Gm to 10 mg Gm	1 mg ml
Carbomycin (Magnamycin®)	50 mg lb per day 4 × daily							
Neomycin	50 mg lb per day 4 × daily	4 mg lb per day 4 × daily				50 mg ml. 1 ml b i d	2 mg ml 5 mg Gm	2 mg ml
Polymyxin	5-10 mg/lb per day 4 × daily	1 mg lb per day 3 × daily			Under 2 yr. —2 mg per day Over 2 yr —5 mg per day 5 mg ml		5 mg ml.	1 mg ml.
Bacitracin	800 U lb per day 4 × daily	300 600 U lb per day 3 × daily Never over 50 000 U daily			1000 U ml 500 to 5000 U daily		500 U ml	1000 U ml
Gantrisin®	60 mg lb per day 4 × daily	60 mg lb per day 3 × daily	60 mg lb daily 50 mg ml	60 mg lb per day 25 mg ml			40 mg ml	
Sulfadiazine or Sodium Sulfadiazine	60 mg lb per day 4 × daily		60 mg lb per day 50 mg ml	60 mg lb per day 25 mg ml			50 mg Gm	
Sulfasuxidine®	100 mg/lb per day 4 × daily							
Furadantin®	3 mg lb per day 4 × daily							
Isoniazid (INH)	3 4 mg lb per day 4 × daily							
Para-aminosalicylic Acid (PAS)	2 5 Gm per day 4 × daily		30 mg ml					

* From Silver, Kempe and Bruyn Handbook of Pediatrics Lange Medical Publications 1955

TABLE 4 — ANTIBIOTIC AND CHEMOTHERAPEUTIC DOSAGE TABLE*

		Parenteral			Topical			
Drugs	*Oral*	*Intra-muscular*	*Intra-venous*	*Subcu-taneous*	*Intra-thecal Intra-ventricular*	*Aerosol*	*Eye and Skin*	*Intra-pleural Intra-articular*
Penicillin	100 000 U to 300 000 U 5 × daily ½ hr before meals	1000 U/lb per day or 100,000 to 300,000 U daily	1000 U/lb per day		1000 U/ml 5 10 ml q 12 hr	50 000 U/ml 1 ml b i d	500 U/ml to 1000 U/ml	10,000 U/ml to 20 000 U/ml
Bacillin®	300,000 U (4 × daily) anytime	600,000 U single injection or 1,200 000 U (all purpose)						
Streptomycin, Dihydrostreptomycin	20 mg /lb per day 4 × daily	10 20 mg/lb per day 1 or 2 × daily			Streptomycin only 0 5 mg/lb or 20 mg per day	150 mg/ml 1 ml b i d	50 mg/ml	50 mg /ml
Chlortetracycline (Aureomycin®)	10 mg /lb per day 4 × daily		6 mg /lb per day 1 mg /ml				5 mg /ml 30 mg /Gm	5 mg /ml
Oxytetracycline (Terramycin®)	10 mg/lb per day 4 × daily	6 mg /lb per day 2 × daily	6 mg /lb per day			50 mg /ml in 75% propylene glycol 1 ml b i d	5 mg /ml 30 mg /Gm	5 mg /ml
Tetracycline (Achromycin®) (Tetracyn®) (Polycycline®) (Steclin®)	10 mg/lb per day 4 × daily	6 mg /lb per daily 2 × daily	6 mg/lb per day 1 mg/ml					
Chloramphenicol (Chloromycetin®)	20 mg/lb daily up to 60 mg/lb per day 4 × daily	30 60 mg/lb daily intramuscularly 2 × daily	15 30 mg/lb daily 5 mg /ml	15 30 mg/lb daily 2 5 mg/ml			5 mg /ml 10 mg /Gm	5 mg /ml

Erythromycin (*Erythrocin*®) (Ilotycin®)	20-30 mg/lb daily 4 × daily		16 mg/lb per day 0.5-1 mg/ml				5 mg/Gm to 10 mg/Gm	1 mg/ml
Carbomycin (Magnamycin®)	50 mg/lb per day 4 × daily							
Neomycin	50 mg/lb per day 4 × daily	4 mg/lb per day 4 × daily				50 mg/ml, 1 ml b.i.d.	2 mg/ml 5 mg/Gm	2 mg/ml
Polymyxin	5-10 mg/lb per day 4 × daily	1 mg/lb per day 3 × daily			Under 2 yr.—2 mg per day. Over 2 yr.—5 mg per day. 5 mg/ml		5 mg/ml	1 mg/ml
Bacitracin	800 U/lb per day 4 × daily	300-600 U/lb per day 3 × daily. Never over 50,000 U daily			1000 U/ml 500 to 5000 U daily		500 U/ml	1000 U/ml
Gantrisin®	60 mg/lb per day 4 × daily	60 mg/lb per day 3 × daily	60 mg/lb daily. 50 mg/ml	60 mg/lb per day. 25 mg/ml			40 mg/ml	
Sulfadiazine or *Sodium* Sulfadiazine	60 mg/lb per day 4 × daily		60 mg/lb per day. 50 mg/ml	60 mg/lb per day. 25 mg/ml			50 mg/Gm	
Sulfasuxidine®	100 mg/lb per day 4 × daily							
Furadantin®	3 mg/lb per day 4 × daily							
Isoniazid (INH)	3-4 mg/lb per day 4 × daily							
Para-aminosalicylic Acid (PAS)	2-8 Gm per day 4 × daily		10 mg/ml					

* From Silver, Kempe, and Bruyn: Handbook of Pediatrics. Lange Medical Publications, 19[illegible]

TABLE 4.—ANTIBIOTIC AND CHEMOTHERAPEUTIC DOSAGE TABLE*

Drugs	Oral	Parenteral: Intra-muscular	Parenteral: Intra-venous	Parenteral: Subcu-taneous	Topical: Intra-thecal Intra-ventricular	Topical: Aerosol	Topical: Eye and Skin	Topical: Intra-pleural Intra-articular
Penicillin	100,000 U to 300,000 U 5 × daily ½ hr before meals	1000 U/lb per day or 100,000 to 300,000 U daily	1000 U/lb per day		1000 U/ml 5-10 ml q 12 hr	50 000 U/ml 1 ml b.i.d.	500 U/ml to 1000 U/ml	10,000 U/ml to 20,000 U/ml
Bacillin®	300,000 U (4 × daily) anytime	600,000 U single injection or 1,200 000 U (all purpose)						
Streptomycin, Dihydrostreptomycin	20 mg/lb per day 4 × daily	10-20 mg/lb per day 1 or 2 × daily			Streptomycin only 0.5 mg/lb or 20 mg per day	150 mg/ml 1 ml b.i.d.	50 mg/ml	50 mg/ml
Chlortetracycline (Aureomycin®)	10 mg/lb per day 4 × daily		6 mg/lb per day 1 mg/ml				5 mg/ml 30 mg/Gm	5 mg/ml.
Oxytetracycline (Terramycin®)	10 mg/lb per day 4 × daily	6 mg/lb per day 2 × daily	6 mg/lb per day			50 mg/ml in 75% propylene glycol 1 ml b.i.d.	5 mg/ml 30 mg/Gm	5 mg/ml
Tetracycline (Achromycin®) (Tetracyn®) (Polycycline®) (Steclin®)	10 mg/lb per day 4 × daily	6 mg/lb per daily 2 × daily	6 mg/lb per day 1 mg/ml					
Chloramphenicol (Chloromycetin®)	20 mg/lb daily up to 60 mg/lb per day 4 × daily	30-60 mg/lb daily intramuscularly 2 × daily	15-30 mg/lb daily 5 mg/ml	15-30 mg/lb daily 2.5 mg/ml			5 mg/ml 10 mg/Gm	5 mg/ml

Erythromycin (Erythrocin*) (Ilotycin*)	20-30 mg/lb daily 4 × daily		10 mg/lb per day 0.5-1 mg/ml				5 mg/Gm to 10 mg/Gm	1 mg/ml
Carbomycin (Magnamycin*)	50 mg/lb per day 4 × daily							
Neomycin	50 mg/lb per day 4 × daily	4 mg/lb per day 4 × daily				50 mg/ml 1 ml b.i.d.	2 mg/ml 5 mg/Gm	2 mg/ml
Polymyxin	5-10 mg/lb per day 4 × daily	1 mg/lb per day 3 × daily			Under 2 yr.—2 mg per day. Over 2 yr.—5 mg per day 5 mg/ml		5 mg/ml.	1 mg/ml.
Bacitracin	800 U/lb per day 4 × daily	300-600 U/lb. per day 3 × daily. Never over 50,000 U daily			1000 U/ml 500 to 2000 U daily		500 U/ml	1000 U/ml
Gantrisin*	60 mg/lb per day 4 × daily	60 mg/lb per day 3 × daily	60 mg/lb daily 50 mg/ml	60 mg/lb per day 25 mg/ml			40 mg/ml	
Sulfadiazine or Sodium Sulfadiazine	60 mg/lb per day 4 × daily		60 mg/lb per day 50 mg/ml	60 mg/lb per day 25 mg/ml			50 mg/Gm	
Sulfasuxidine*	100 mg/lb per day 4 × daily							
Furadantin*	3 mg/lb per day 4 × daily							
Isoniazid (INH)	3-4 mg/lb per day 4 × daily							
Para-aminosalicylic Acid (PAS)	2-8 Gm per day 4 × daily		[illegible]0 mg/ml					

* From Silver, Kempe and Bruyn [illegible]

TABLE 4 — ANTIBIOTIC AND CHEMOTHERAPEUTIC DOSAGE TABLE*

Drugs	Oral	Parenteral			Topical			
		Intra-muscular	*Intra-venous*	*Subcu-taneous*	*Intra-thecal Intra-ventricular*	*Aerosol*	*Eye and Skin*	*Intra-pleural Intra-articular*
Penicillin	100 000 U to 300 000 U 5 × daily ½ hr before meals	1000 U/lb per day or 100,000 to 300,000 U daily	1000 U lb per day		1000 U ml 5 10 ml q 12 hr	50 000 U ml 1 ml b i d	500 U ml to 1000 U ml	10,000 U ml to 20,000 U ml
Bacillin®	300 000 U (4 × daily) anytime	600 000 U single injection or 1,200,000 U (all purpose)						
Streptomycin, Dihydrostreptomycin	20 mg lb per day 4 × daily	10 20 mg lb per day 1 or 2 × daily			Streptomycin only 0 5 mg lb or 20 mg per day	150 mg ml 1 ml b i d	50 mg ml	50 mg /ml
Chlortetracycline (Aureomycin®)	10 mg /lb per day 4 × daily		6 mg /lb per day 1 mg ml				5 mg /ml 30 mg /Gm	5 mg /ml
Oxytetracycline (Terramycin®)	10 mg lb per day 4 × daily	6 mg lb per day 2 × daily	6 mg /lb per day			50 mg /ml in 75% propylene glycol 1 ml b i d	5 mg /ml 30 mg /Gm	5 mg /ml
Tetracycline (Achromycin®) (Tetracyn®) (Polycycline®) (Steclin®)	10 mg /lb per day 4 × daily	6 mg /lb per daily 2 × daily	6 mg /lb per day 1 mg ml					
Chloramphenicol (Chloromycetin®)	20 mg /lb daily up to 60 mg lb per day 4 × daily	30 60 mg lb daily intramuscularly 2 × daily	15 30 mg /lb daily 5 mg ml	15 30 mg /lb daily 2 5 mg ml			5 mg /ml 10 mg /Gm	5 mg /ml

desire to use measures by which he is decreasing still further the small danger of such incidents. He may therefore be justified in using antibiotics when he decides that he is dealing with any respiratory infection which is severe enough to produce a moderate degree of fever and which has caused the child to appear ill. Furthermore, if it is known that a particular child generally reacts badly to infection or that his general health and nutrition are below par, the case for using antibiotics is strengthened. If, on the other hand, the child usually recovers well from infection and if his nutrition and general condition are good, the physician may decide at least to postpone antibiotics and to employ nonspecific measures. It cannot be denied that certain intangible factors such as the attitude of the parents, and the general custom regarding antibiotic therapy in the community may also enter into the decision. Evaluation of such intangibles involves the art of the practice of medicine. We must avoid arbitrary administration of antibiotics to every child who has fever, regardless of other considerations. The substitution of this practice for judgment and thought may cloud a proper understanding of the illness and lead to eventual harm to the patient.

SELECTION OF AN ANTIBIOTIC

Under ordinary conditions the choice of an antibiotic must depend at the start of treatment at least upon clinical judgment alone. Usually treatment must be instituted before the etiologic agent has been identified. Thus, in most cases, one must assume that the organism responsible for an attack of tonsillitis is a hemolytic streptococcus and we must choose the antibiotic accordingly. If an attempt is to be made to identify the causative organism, suitable material must be collected *before starting the antibiotic.* After that it must be remembered that one is entering upon a trial run of the drug only, and we must be prepared to change our course if the subsequent identification of the causative organism

is the case when the physician is able to recognize the presence of a bacterial or rickettsial infection which from the beginning involves a risk of death or serious injury to the patient. For example, if the physician finds clinical evidence of infection with meningococci, antibiotic and chemotherapeutic drugs should be employed at once Similar reasoning demands that antibiotics be administered for the treatment of Rocky Mountain spotted fever at the earliest possible moment Although the need is less urgent, we believe that antibiotics should be used whenever there is good reason on clinical grounds to believe that a beta hemolytic streptococcal infection is present This conclusion is based upon the knowledge that these organisms tend to invade tissues adjacent to the site of the original infection, and is supported by evidence that prompt treatment of streptococcal disease decreases the possibility of the occurrence of rheumatic fever and nephritis

Often the site of the infection makes the use of antibiotics essential For example they must be employed when there is infection of meninges, pleura, middle ear, bones or endocardium The same consideration is true when bacteremia or septicemia is present

A much more difficult decision must be made when a child is suffering from an infection which presents little risk to his life and which is not liable to cause him permanent injury The physician encounters such cases daily in caring for children with mild upper respiratory infections He is unable to determine by physical examination whether such infections are viral in origin, whether they are due to streptococci, or to other organisms In such circumstances, he must be aware that the goal of therapy is mainly that of restoring the child more rapidly to complete health than would be the case if the illness were permitted to run its natural course The physician is attempting to shorten the duration of the child's discomfort and to lessen the period of anxiety of his parents. Since even the mildest sort of bacterial or viral infection may be followed by sequelæ, the doctor may

desire to use measures by which he is decreasing still further the small danger of such incidents He may therefore be justified in using antibiotics when he decides that he is dealing with any respiratory infection which is severe enough to produce a moderate degree of fever and which has caused the child to appear ill. Furthermore, if it is known that a particular child generally reacts badly to infection or that his general health and nutrition are below par, the case for using antibiotics is strengthened If, on the other hand, the child usually recovers well from infection and if his nutrition and general condition are good, the physician may decide at least to postpone antibiotics and to employ nonspecific measures. It cannot be denied that certain intangible factors such as the attitude of the parents, and the general custom regarding antibiotic therapy in the community may also enter into the decision. Evaluation of such intangibles involves the art of the practice of medicine We must avoid arbitrary administration of antibiotics to every child who has fever, regardless of other considerations The substitution of this practice for judgment and thought may cloud a proper understanding of the illness and lead to eventual harm to the patient.

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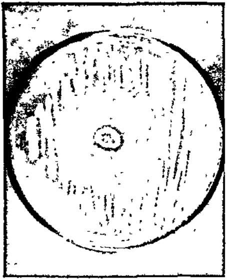
requires it Fortunately, in most instances, the clinical course of the patient will indicate within twenty-four or thirty-six hours whether our choice has been sound In such *circumstances laboratory data would merely confirm the* correctness of our judgment, but in every-day practice, the patient's response to treatment may be the only data available One should bear in mind that when evidence of improvement is not obtained promptly, perhaps an ineffective antibiotic has been chosen and a change should be made Persistence in the use of an antibiotic which has failed after a fair trial with adequate dosage should be avoided.

There is usually little need for the determination of sensitivity to antibiotics when we are dealing with very sensitive organisms such as pneumococci, hemolytic streptococci or meningococci However, when more resistant organisms such as staphylococci, Streptococcus fecalis, Pseudomonas æruginosa, or proteus strains are present, assays of sensitivity to antibiotics may be of the utmost importance

The most important factor in the selection of an antibiotic is its effectiveness However, a number of other factors also enter into the decision When two drugs of nearly equal efficacy are under consideration, the one less likely to produce toxic effects will naturally be chosen In a general way, if all other factors are equal, the antibiotic which is effective when given by mouth is to be preferred over one which must be administered by injection Consideration must be given to the concentration of the antibiotic which can be attained in the patient's blood and other body fluids The cost of the drugs under consideration also may be of importance.

After an antibiotic, has been chosen questions of **dosage** and **duration of treatment** must be decided A great many factors will enter into these decisions. When one is dealing with a highly susceptible microorganism, dosage may be curtailed and the period of treatment shortened. On the other hand, *maximum* dosage and prolonged treatment are necessary when abscess formation interferes with diffusion of the antibiotic. Thus, subacute *endocarditis, purulent otitis media,*

PLATE I



Reproduction of Fleming's original staphylococcus culture plate accidentally contaminated with *Penicillium notatum* (By permission of the copyright owner, Sharp & Dohme, Inc, as originally presented in their February, 1946, "Seminar")

and osteomyelitis require intensive treatment of relatively long duration. An antibiotic of low toxicity may be employed for long periods, while a relatively toxic one such as polymyxin must be used for a short time only. Similarly, nausea and vomiting often place a limit upon the quantity of aureomycin which may be used.

Penicillin

Penicillin, the least expensive antibiotic, is generally the one of choice for infections caused by Gram-positive organisms with the exception of staphylococci. It is the most effective antibiotic against hemolytic streptococci and pneumococci, and also for the treatment of gonorrhea and syphilis. In combination with streptomycin, it is the most effective agent against Streptococcus fecalis. Details regarding the use of penicillin in various diseases such as bacterial meningitis are described in the appropriate chapters on those subjects.

It is a remarkable fact that no significant resistance to penicillin has developed among strains of pneumococci, beta hemolytic streptocci, gonococci and Treponema pallidum. Penicillin continues to be as effective against these organisms as it was when first employed against them. Unfortunately, this is not true for pathogenic staphylococci, most strains of which are no longer sensitive to penicillin. The proportion of penicillin resistant strains of staphylococci isolated from patients and attendants in hospitals is much higher than that obtained from the general population. The present refractory state of most staphylococci is probably due to the elimination of penicillin sensitive strains which has permitted the resistant penicillinase-producing strains to spread freely. Therefore, penicillin should no longer be the first antibiotic chosen for infections caused by Staphylococcus aureus.

Penicillin is probably the most effective drug for reducing the incidence of recurrences in rheumatic fever by preventing

hemolytic streptococcal infections. It is superior to the sulfa drugs for this purpose because sulfonamide-resistant hemolytic streptococci are much more frequently encountered than are penicillin-resistant strains Buffered tablets of potassium penicillin G, and tablets of Bicillin are now most often used for rheumatic fever patients. The usual dose is one tablet (200,000 units) given once a day Bicillin suspensions have also been given in a dosage of 1 teaspoonful (300,000 units) once daily One depository injection of 1,200,000 units of Bicillin given once a month has also been used with apparent success

Method of Administration—The method of administration of penicillin has undergone a change in the past few years There is a trend toward oral therapy and in general, it may be stated that penicillin given by mouth is sufficiently effective to be the method of choice in all but the most severe types of infection Since only 20 to 30 per cent of penicillin given by mouth is absorbed into the plasma, the dosage must be three to five times as large as the dose given by intramuscular injection Streptococcal pharyngitis and tonsillitis, scarlet fever, erysipelas and cervical adenitis may be treated by the oral route, so also Pneumococcic pneumonia of average severity Vincent's angina is readily controlled in the same way. On the other hand, endocarditis, septicemia, purulent otitis media and meningitis should be treated by parenteral injection of penicillin. When the infecting organism is relatively insensitive to penicillin, the drug should be given by injection regardless of the site of infection

There are available a number of forms of penicillin for oral use. These include the following:

1. [illegible]
2. [illegible] and small children.
3. Tablets of dibenzylethylenediamine dipenicillin-G (Bicillin*), containing 200,000 units per tablet.

4 A liquid suspension of dibenzylethylenediamine dipenicillin-G (Bacillin oral suspension), containing 300,000 units per teaspoon.*

5 There has recently been introduced a new form of penicillin, phenoxymethyl penicillin (penicillin V) which is much more stable than other forms of penicillin in acid media such as that of the stomach Because of this factor, it appears that penicillin V gives somewhat higher blood levels than do the other oral preparations available Penicillin V is available in *tablet form (200,000 units per tablet) and in a liquid* preparation (200,000 units per teaspoonful).

All of the forms of penicillin intended for oral administration are given in dosage varying from 200,000 to 600,000 units three or four times a day for adults and older children For young children and for infants, the dosage is 10,000 to 15,000 units per kilogram of body weight every six hours. When given orally, penicillin should be administered before meals since all preparations generally produce higher blood levels when given in this way, however, they are also effective when given after meals

The following injectable penicillin products are in general use.

1. Procaine penicillin-G in aqueous suspension in dosage of 300,000 to 600,000 units once or twice daily
2. Crystalline potassium penicillin-G, in aqueous solution (1 gram of crystalline penicillin-G equals 1 5 million units), in dosage varying from 50,000 to 500,000 units every four hours depending upon the infection being treated.
3. Procaine penicillin-G (3 parts) combined with crystalline potassium penicillin-G (1 part), given in dosage of 300,000 to 600,000 units once or twice daily.

4. Procaine penicillin-G in oil and aluminum monostearate, 300,000 to 600,000 units are given every third day
5. Dibenzylethylenediamine dipenicillin-G (Bicillin*) has its greatest use in prevention of streptococcal infections among persons who have suffered an attack of rheumatic fever. For this purpose, 1,200,000 units are given by intramuscular injection once a month. For treatment of streptococcic infections, a single dose of 600,000 units is given intramuscularly.

Procaine penicillin is the preparation most often used for intramuscular injection, it cannot be given intravenously. It is usually given once or twice daily, and gives very satisfactory plasma concentrations of penicillin. In treating severe infections it should be remembered that the tissue concentration of penicillin is on the average only 25 or 50 per cent of that in the plasma.

When crystalline potassium penicillin is used, injections should be made three or four times daily. This preparation is usually given intramuscularly, but it may be given intravenously.

Procaine penicillin-G combined with crystalline potassium penicillin-G may be used to obtain a more prompt peak in plasma penicillin level than can be obtained with procaine penicillin alone.

Procaine penicillin in oil and aluminum stearate has been used to *give prolonged penicillinemia of relatively low concentration* for seventy-two hours or even longer. We no longer use this preparation because of the possibility that the oil which it contains may increase the danger of sensitization to penicillin. In addition, it appears that Bicillin may be more useful when prolonged penicillinemia of low concentration is desirable, as in the treatment of syphilis and for antistreptococcal prophylaxis in rheumatic fever. When given in a single injection of 1,200,000 units a detectable low concentration of penicillin (0.02 units per ml or more) persists in the plasma for twenty-one days in most subjects, and for

twenty-eight days in some. Streptococcal infections of various types, and pneumonia have been treated successfully with a single injection of Bicillin. We do not believe, however, that this form of treatment should be the method of choice at this time.

As has been stated in the chapter on meningitis, there is good opinion that *intrathecal penicillin therapy* is unnecessary except in very rare instances. When it is required, only crystalline potassium penicillin dissolved in 0.85 per cent sodium chloride solution should be used. Dosage should not exceed 1,000 units for infants, and no more than 10,000 units should be used for adults. A concentration above 1,000 units of penicillin per cc. should not be given intrathecally.

The Tetracycline Compounds

Aureomycin (chlortetracycline), terramycin (oxytetracycline) and tetracycline itself are all tetracycline compounds. Aureomycin was the first of these antibiotics to be discovered (1948). It is an antibiotic substance produced by Streptomyces aureofaciens. Two years later, terramycin, obtained from Streptomyces rimosus, was introduced. Both antibiotics proved to be effective against many Gram-positive as well as Gram-negative organisms, against Rickettsiae, and against organisms of the lymphogranuloma-psittacosis group. They are therefore "broad spectrum" antibiotics. Aureomycin and terramycin are very similar in their action against bacteria and are in general effective against the same organisms. Conversely, an organism resistant to one of them is almost invariably resistant to the other also. Their toxic effects are also quite similar. In 1952, the two drugs were shown to be very similar in chemical structure. The compounds are identical except that aureomycin contains a chlorine atom and terramycin does not, while terramycin has a hydroxyl group and aureomycin does not. Aureomycin has, therefore, been termed chlortetracycline and terramycin is oxytetracycline.

4 Procaine penicillin-G in oil and aluminum monostearate, 300,000 to 600,000 units are given every third day

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When crystalline potassium penicillin is used, injections should be made three or four times daily This preparation is usually given intramuscularly, but it may be given intravenously

Procaine penicillin-G combined with crystalline potassium penicillin-G may be used to obtain a more prompt peak in plasma penicillin level than can be obtained with procaine penicillin alone

Procaine penicillin in oil and aluminum stearate has been used to give prolonged penicillinemia of relatively low concentration for seventy-two hours or even longer. We no longer use this preparation because of the possibility that the oil which it contains may increase the danger of sensitization to penicillin. In addition, it appears that Bicillin may be more useful when prolonged penicillinemia of low concentration is desirable, as in the treatment of syphilis and for antistreptococcal prophylaxis in rheumatic fever. When given in a single injection of 1,200,000 units a detectable low concentration of penicillin (0 02 units per ml. or more) persists in the plasma for twenty-one days in most subjects, and for

a subcommittee of the Medical Research Council of Great Britain states that 22 to 32 per cent of patients treated with terramycin and aureomycin showed toxic symptoms, as compared with 6 per cent of penicillin treated patients. However, fever and eruptions are much less likely to occur with tetracycline drugs than with penicillin. In contrast to penicillin, there have been no reports of fatal anaphylactic reactions with the tetracyclines. It should be noted that a survey in 1952 revealed 34 cases of anemia which may have been caused by aureomycin and terramycin.

The similarities of aureomycin, terramycin and tetracycline are so great that they may be regarded, with minor exceptions, as a single antibiotic, and relative costs are the same. Thus, if an infection has not been brought under control with terramycin, little will usually be gained by changing to aureomycin or vice versa.

The tetracycline drugs are usually given by mouth in four or six daily doses. For infections of average severity, a total of 20 to 25 mg. per kilogram of body weight is given daily. The drugs are dispensed in capsules for adults and older children, and suspensions of the drugs in flavored liquids are used for infants and small children. Preparations for intramuscular and intravenous use are also available for treatment of severe infections or for patients who are too ill to take the drugs by mouth. The dosage for intramuscular and intravenous use varies from 2 to 6 mg. per kilogram of body weight, given three times daily.

Erythromycin

Erythromycin* is an effective antibiotic produced by Streptomyces erythreus obtained from soil from the Philippines. It was prepared and introduced for general use in 1952. Erythromycin is a crystalline basic compound which readily forms acid salts. *In vitro* experiments showed erythromycin to be active against many Gram-positive organisms as

* Erythromycin is sold under the trade names Erythrocin® and Ilotycin ®

In 1953, a third antibiotic member of the group, tetracycline,* was formed by removing the chlorine atom from aureomycin. This new antibiotic was also obtained at about the same time from the filtrate of a culture of streptomycetes contained in a sample of Texas soil.

These tetracycline compounds are very useful antibiotics. Their effect upon Gram-positive organisms is similar to that of penicillin, but their effectiveness is probably of somewhat lesser degree. At concentrations usually attained in plasma and tissues, the tetracycline drugs are bacteriostatic, while penicillin is bactericidal. In numerous clinical tests the tetracycline drugs have been proven to be highly effective in the treatment of beta hemolytic streptococcal and pneumococcal infections of every type, and their effectiveness in scarlet fever, tonsillitis, otitis media, and pneumonia have been demonstrated beyond question. They have been shown to be effective also in prophylaxis against streptococcal infections among rheumatic fever patients. They may be regarded as a suitable substitute for penicillin against infections with Gram-positive cocci when sensitivity to penicillin or some other considerations preclude the use of this drug.

The tetracyclines are the most effective agents available [illegible]

influenzæ. In combination with streptomycin they give the best results obtainable in the treatment of brucellosis.

When first introduced the tetracycline drugs were found to be very useful against staphylococci which were resistant to penicillin. However, as with penicillin, the use of the tetracyclines has been so great that strains of pathogenic staphylococci encountered today are very much less likely to be sensitive to these antibiotics than was formerly the case.

Nausea, vomiting, and diarrhea are by far the most common toxic symptoms caused by the tetracycline drugs. A report of

* Tetracycline is sold under various trade names including Achromycin,® Tetracyn,® Steclin,® and Panmycin.®

It should be noted that erythromycin tends to diffuse poorly into walled off abscesses and into empyema cavities. In overwhelming staphylococcal infections with septicemia it has been recommended that it be combined with bacitracin.

Erythromycin is a drug of relatively low toxicity. Its average lethal dose for mice is nearly 2 grams per kilogram of body weight. In man it causes less difficulty than the tetracycline drugs. However, abdominal cramps and diarrhea do occur in an appreciable number of patients. Erythromycin is available in enteric coated tablets, and in suspension which is suitable for small children and infants. The usual total daily dose is 20 to 25 mgm. per kilogram of body weight given in four equally divided doses.

Streptomycin and Dihydrostreptomycin

Streptomycin is an antibiotic produced by certain strains of the actinomycete, Streptomyces griseus, or "ray fungus." At the present time this antibiotic and its derivative, Dihydrostreptomycin, are used chiefly in the treatment of tuberculosis. Danger of injury to the eighth cranial nerve and the frequency with which streptomycin-resistant strains emerge have combined to limit the usefulness of these antibiotics. Even in those cases in which other infecting bacteria are initially sensitive, the possibility is great that they will be resistant in forty-eight to ninety-six hours. Hence, except in the treatment of tuberculosis, streptomycin should be the first antibiotic chosen in only a few conditions. These include its use in combination with penicillin in the treatment of subacute endocarditis due to enterococci and with aureomycin for treatment of brucellosis. Streptomycin should rarely be used for other infections unless laboratory facilities are available for determination of the specific sensitivity of the infecting organism to the antibiotic. When such facilities are at hand, occasions will at times be found which make the use of streptomycin essential.

well as a number of Gram-negative bacteria Sensitive species include Diplococcus pneumoniæ (including strains resistant to sulfonamides), Staphylococcus aureus (including some penicillin-resistant strains), hemolytic streptococci, Streptococcus viridans, meningococci, gonococci, brucella and Hemophilus influenzæ Erythromycin was also found to be effective experimentally against lymphogranuloma venereum, and Rickettsiæ Haight and Finland reported that erythromycin in laboratory experiments appeared to be as active as penicillin against Gram-positive organisms, and more active than the tetracyclines against such bacteria Its activity in the laboratory against Hemophilus influenzæ is similar to that of the tetracyclines, but it is less active than these drugs against coliform organisms Erythromycin is ineffective against Proteus vulgaris and Pseudomonas æruginosa

Erythromycin has been used successfully in the treatment of human disease caused by beta hemolytic streptococci, pneumonococci, staphylococci, Hemophilus influenzæ, and gonococci Vincent's stomatitis, brucellosis, lymphogranuloma venereum, diphtheria carrier state, and syphilis have also been treated satisfactorily However, erythromycin is apparently inferior to other antibiotics for many of the infections listed above, its main usefulness being in the treatment of Gram-positive cocci, particularly staphylococci, and to a lesser extent, pneumococci and hemolytic streptococci Early laboratory experience with erythromycin showed that very few strains of staphylococci were resistant to it However, as erythromycin has been used more and more widely, an increasing number of staphylococcus strains resistant to it have been found, and clinical experience has paralleled these laboratory findings. Because erythromycin is less effective against other infections than are other antibiotics, and because its generalized use leads to the growth of resistant staphylococci, it would seem wise to use erythromycin against pathogenic staphylococci only. In this way emergence of erythromycin-resistant strains of staphylococci will be retarded, and the superior value of the drug in staphylococcal infections may be preserved.

receiving sulfonamides, tetracycline drugs, antihistaminics and antipyretics. It has also been stated that the incidence of bone marrow depression among persons treated with chloromycetin was actually less than that to be expected among normal populations not receiving this drug. Hence, chloromycetin should be used whenever it is clearly the antibiotic of choice for the treatment of a given infection such as those caused by Hemophilus influenzæ or the Salmonella organisms, but the tetracyclines may be first chosen for the treatment of an infection for which they and chloromycetin are equally effective. However, when the tetracyclines have failed or laboratory sensitivity tests reveal a great superiority of chloromycetin, the latter drug should be employed without hesitation.

Chloromycetin is available as a solid in capsules and as a liquid suspension (chloromycetin palmitate). The usual oral dosage of chloromycetin is 30 to 50 mgm. per kilogram of body weight per day given in 4 to 6 divided doses. A preparation for intravenous use and still another for intramuscular injection are also available. When used intravenously or intramuscularly, injections are usually made every eight hours with a total dosage of 20 to 50 mgm. per kilogram of body weight.

Polymyxin, Neomycin and Bacitracin

Because of their toxicity these three antibiotics have limited usefulness, but when properly used they may save life when other antibiotics are ineffective.

Polymyxin.—The polymyxins are basic polypeptides derived from the soil organism Bacillus polymyxa. There are at least five polymyxins which have been named A, B, C, D, and E. They differ in their amino acid makeup but all contain diamino butyric acid. Polymyxin B is commercially available (Aerosporin*). It is marketed as a crystalline powder in sterile ampoules in 50-mgm. quantities. Polymyxin is strongly bactericidal against Gram-negative organ-

Streptomycin is usually given intramuscularly. In the treatment of tuberculous meningitis, it may be administered intrathecally. When given by mouth it is not absorbed into the blood in appreciable quantities and is nontoxic

Dosage of streptomycin varies with the severity of the infection and with the age of the patient. For treatment of primary pulmonary tuberculosis in children, a total of 0 3 to 1 0 gram daily is recommended (given by intramuscular injection) Various dosage schedules are used in treating tuberculous meningitis. One of these employs 1 0 gram of streptomycin daily (intramuscularly) regardless of age Emaciated children and small infants are given 0.5 gram twice daily.

Chloromycetin (Chloramphenicol)

Chloromycetin was obtained from a strain of streptomyces isolated by Burkholder. In addition, it has been produced synthetically It is a wide-spectrum antibiotic, effective against a great variety of bacteria including Gram-positive as well as Gram-negative organisms, against Rickettsiæ, and against organisms of the lymphogranuloma venereum-psittacosis group Its effectiveness and cost is similar to that of the tetracycline drugs and it produces fewer gastrointestinal reactions than these compounds For these reasons it was used very widely for a number of years. However, reports in 1952 which indicated that it might produce deleterious effects on the bone marrow of susceptible persons brought about a sharp curtailment of its use. It was reported that persons receiving chloromycetin had developed various blood dyscrasias including aplastic anemia, granulocytopenia, and thrombocytopenic purpura. A survey by Welch and his co-workers indicated that the incidence of aplastic anemia was approximately 1 case in 40,000. No constant relationship was demonstrated between the occurrence of bone marrow injury and the dose, duration of therapy, or allergic diathesis of the patient Welch also pointed out that aplastic anemia may occur among patients

receiving sulfonamides, tetracycline drugs, antihistaminics and antipyretics. It has also been stated that the incidence of bone marrow depression among persons treated with chloromycetin was actually less than that to be expected among normal populations not receiving this drug. Hence chloromycetin should be used whenever it is clearly the antibiotic of choice for the treatment of a given infection such as those caused by Hemophilus influenzæ or the Salmonella organisms, but the tetracyclines may be first chosen for the treatment of an infection for which they and chloromycetin are equally effective. However, when the tetracyclines have failed or laboratory sensitivity tests reveal a great superiority of chloromycetin, the latter drug should be employed without hesitation.

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isms, but has no effect upon Gram-positive bacteria. It has a marked tendency to cause renal injury. Many patients receiving polymyxin exhibit albuminuria and cylindruria. While these findings do not necessitate removal of the drug, evidence of oliguria does constitute such an indication.

Polymyxin has proven to be of value chiefly for infections due to Pseudomonas æruginosa (Bacillus pyocyaneus). For treatment of urinary and other systemic infections, polymyxin is given by intramuscular injection. The total daily dosage used is 2 to 4 mgm. per kilogram of body weight. This dose should be divided into 4 to 6 doses. Since the injections are quite painful, it is best to give polymyxin in a 1 or 2 per cent solution of procaine.

Neomycin.—Neomycin is a basic crystalline antibiotic obtained from Streptomyces fradiæ. In very low concentrations it is bactericidal against most Gram-negative organisms. In higher concentration it is effective against many Gram-positive cocci, and against M. tuberculosis also. Its spectrum is similar to that of streptomycin, but neomycin-resistant organisms do not appear as readily as do streptomycin-resistant strains.

Neomycin resembles dihydrostreptomycin in that it first damages the auditory rather than the vestibular portion of the eighth cranial nerve. Neomycin is also nephrotoxic, having an action on the kidney which is similar but less marked than polymyxin and bacitracin. When oliguria occurs in the course of neomycin therapy, the drug should be discontinued.

Of the antibiotics which have had extensive clinical trial, neomycin is the most effective antibiotic against Proteus vulgaris infection. The drug is given intramuscularly in 1 to 2 per cent procaine solution. The total daily dosage is 10 mgm. (2,000 units) per kilogram of body weight. This dose is divided into 4 equal doses.

Bacitracin.—Bacitracin is a basic polypeptide obtained from a strain of Bacillus subtilus. It is bactericidal for most Gram-positive organisms. It resembles polymyxin in its

tendency to cause kidney damage Albuminuria and casts are to be expected with this drug, but oliguria or a rise in blood non-protein nitrogen are indications for immediate withdrawal of the drug

Bacitracin appears to have its main usefulness in combination with penicillin in the treatment of resistant bacterial endocarditis, and in the treatment of staphylococcal infections of the central nervous system Bacitracin is injected intramuscularly in a procaine solution. The total daily dosage is 1,000 units per kilogram of body weight, divided into 4 doses It is also used in ointments for local skin infection.

Nystatin (Mycostatin®)—Nystatin is an antibiotic obtained from cultures of streptomyces noursei appears to be of clinical usefulness for the treatment of Candida albicans infections (moniliasis) of the skin, vagina intestine and mouth (thrush) It does not seem to be effective in superficial mycotic infections, other than those due to monilia Its value in generalized moniliasis is equivocal

Nystatin, *in vitro*, inhibits or destroys actively growing fungi, especially the yeast or yeast-like fungi It is most effective against organisms in the vegetative stage, but has little effect upon spores It is inactive against the actinomycetes, and it has no effect upon bacteria

Mycostatin® (Squibb) is available in the form of a powder and tablet for oral administration It is also prepared in tablet form for insertion into the vagina, and in an ointment base for application to the skin. A preparation suitable for intramuscular injection can also be obtained

For intestinal moniliasis the dosage used has generally been 500,000 units, three times daily For the treatment of thrush, Mycostatin® powder, 100,000 units given by mouth three times daily, has been used with favorable results In other cases local application of Mycostatin® ointment has been effective Vaginal moniliasis has been favorably influenced by oral therapy as well as by vaginal medication Definite improvement or cure has been noted in the great

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agent against bacterial infections was not thought of until 1913 when Eisenberg, working with one of the azo dyes (chrysoidine), discovered its bactericidal action *in vitro*. In 1917 Jacobs and Heidelberger, working together on para-aminobenzenesulfonamide, commented upon its bactericidal qualities, but its true significance was lost in the vast quantity of medical literature. In 1932 German chemists prepared "prontosil" and Domagk showed experimentally that this new drug would protect mice against streptococcic infections, and would accomplish remarkable cures in mice experimentally infected with streptococci. In 1933 the drug was used successfully for the first time on a ten-month-old infant with staphylococcus septicemia. Meanwhile in France, work with prontosil confirmed the German reports and in 1936 Fourneau proved that the active chemotherapeutic part of the drug prontosil was para-aminobenzenesulfonamide.

Study of this drug was taken up by research workers in all countries and resulted in the development of a large number of chemotherapeutic compounds related to sulfanilamide—the most important of them being sulfadiazine, sulfamerazine, and Gantrisin* (acetyl sulfisoxazole).

The sulfonamides were the first effective drugs available for streptococcic, pneumococcic and meningococcic infections. However, penicillin, the tetracyclines and erythromycin are much more effective against streptococci and pneumococci, and are to be preferred over sulfonamides in treatment of infections caused by these organisms. The comparative ineffectiveness of sulfonamides is due to two causes: (1) The sulfonamides are bacteriostatic only, while penicillin is bactericidal. (2) Streptococci resistant to sulfonamides have emerged with much greater frequency than have penicillin and tetracycline-resistant strains. Despite their relative inefficiency, sulfonamides are still used by many pediatricians for streptococcal and pneumococcal infections because of their low cost and because they are so well tolerated by children.

majority of patients with cutaneous moniliasis treated with Mycostatin® ointment In some instances improvement has followed use of the drug

Streptomvicin (Albamycin®, Cathocin®) —This recently discovered antibiotic, now undergoing clinical trial, is produced by an actinomycete, *Streptomyces niveus*. Streptonivicin is stable in acid media, and is unaffected by passage through the stomach It is absorbed into the blood after oral administration in very high proportion With equal doses, blood levels are obtained with streptonivicin which are ten times higher than tetracycline, 25 times higher than erythromycin, and 50 times higher than penicillin Peak blood concentrations are reached within two to three hours after an oral dose, and high levels persist for eight hours. Streptonivicin is excreted in the urine as a biologically active material *In vitro* and animal experiments indicate that streptonivicin is active against such Gram-positive organisms as staphylococci, hemolytic streptococcic, pneumococci, and against Gram-negative organisms like *S typhosa* and *Proteus vulgaris* Since a number of antibiotics are effective against the Gram-positive organisms listed, it is probable that the chief usefulness of streptonivicin may be in the treatment of infections with *Proteus vulgaris* Neomycin, the only previously available antibiotic effective against *Proteus vulgaris*, is nephrotoxic in some cases Streptonivicin does not appear to have this defect, its toxicity in general appears to be very low, although drug fever and a rash followed its use in one of our patients.

The oral dose of streptonivicin is 0 6 grams three times daily for adults, and 10 mgm per kilogram of body weight three times daily for children

SULFONAMIDES

History.—Sulfanilamide (para-aminobenzenesulfonamide) was first prepared by Gelmo in 1908 when experimenting with the preparation of azo dyes. However, its use as an

Sulfamerazine is excreted less rapidly than the other drugs and this enables the blood level to remain more constant. Excretion with sulfanilamide is complete in forty-eight hours but with sulfadiazine it is usually seventy-two hours, and with sulfamerazine even longer.

In the administration of the sulfonamides, certain precautions should be followed. The urine should be examined frequently to detect the first sign of kidney involvement, particularly hematuria. A complete blood examination should be done every three or four days because of the slight possibility of the development of agranulocytosis. Fluid should be given freely to minimize the possibility of injury to the urinary tract by crystallization of acetelated sulfonamide compounds.

Toxic Signs and Symptoms.—Each sulfonamide differs somewhat in degree of toxicity, sulfathiazole being the most toxic of those in common use. Such toxic signs and symptoms as nausea, vomiting, fever, headache, rashes of various kinds, visual and auditory disturbances, and weakness constitute a warning signal to the physician, and while they may not be absolute indications for the discontinuance of the drug, it is usually wiser to change to an appropriate antibiotic. The drug must be discontinued at once if hematuria or jaundice occurs. The development of marked neutropenia or agranulocytosis also requires immediate withdrawal of the sulfonamide.

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Sulfonamides remain the drug of choice for infections due to meningococci, including septicemia and meningitis (See Chapter 14, p 417)

Sulfonamides are of greatest use in combination with antibiotics for the treatment of a number of serious infections Thus, they are used with penicillin in the treatment of pneumococcic, streptococcic, and staphylococcic meningitis, and in the treatment of actinomycosis

The sulfonamides are usually given by mouth They are available in tablets and in liquid suspension for this purpose, the most widely used sulfonamides being sulfadiazine, sulfamerazine and Gantrisin * In addition, soluble salts for intravenous and subcutaneous injection may be employed For this purpose sodium sulfadiazine in a 5 per cent solution in distilled water is employed for intravenous therapy and in 1 per cent solution in 0 85 per cent sodium chloride for subcutaneous injection Intravenous and subcutaneous therapy are used only for patients who are critically ill or who are unable to take the drug by mouth Intrathecal administration is not recommended The oral dosage of sulfonamides varies greatly with the severity of the infection. For such infections as streptococcal tonsillitis and for scarlet fever, a daily dosage of 0 07 to 0 10 grams per kilogram of body weight, divided into 4 doses, may be given. For meningococcic meningitis from 0 1 to 0 15 grams per kilogram of body weight is customary When the drug is given subcutaneously about two-thirds of the oral dosage is used. The intravenous dose usually given is 0 004 gram per kilogram of body weight every eight hours For mild infections a drug concentration of 5 to 6 mgm per 100 cc of blood is sufficient, but for the treatment of meningitis, a drug concentration of 12 to 16 mgm. per cent is necessary.

The sulfonamides are absorbed from the gastro-intestinal tract, mainly the large and small intestine and they are readily distributed throughout all the body fluids The drugs are excreted mainly by the kidneys, but traces may be found in saliva, sweat, gastric secretions, and breast milk.

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antiseptics. On the other hand, cold kills slowly, and the bacilli may survive for weeks in ice. In milk and water they also survive for long periods. Dried membrane may contain toxic living bacilli for several months, but when finely distributed by a spray the bacilli die out in two days or less in an ordinary sun-lit room.

The sulfonamides have no effect on the diphtheria bacillus or its toxin. Most strains of diphtheria bacilli are sensitive to penicillin as judged by *in vitro* tests, and similar effectiveness is displayed by the tetracycline drugs. However, attempts to use antibiotics to protect guinea pigs against infection with *C. diphtheriæ* have yielded equivocal results.



FIG. 5 —One of the very characteristic forms of diphtheria bacilli from blood-serum cultures, showing clubbed ends and irregular stain × 1100 diameters Stain, methylene blue (Park and Williams, Pathogenic Microorganisms)

Identification —Diphtheria bacilli can often be identified in immediate smears prepared with Neisser's or with Ponder's stain, which differentiate the metachromatic granules from the body of the bacilli. They are Gram-positive. A much more certain method of identifying the bacilli is to culture a suspected diphtheritic area onto Loeffler's serum agar slants (a culture medium consisting of a mixture of dextrose, bouillon, and blood serum).

In taking cultures, sterilized cotton swabs twisted on applicators are applied under the margins and on the surface

4

Diphtheria

FROM the Greek Διφθέρα (diphthera) meaning prepared hide, or leather. Hence Bretonneau in 1826 named the disease "la diphthérite," a word shortened many years later (possibly in 1855) to "diphthérie." The word-form "diphtheria" appeared in print in 1856.[1]

Definition.—An acute specific infectious disease caused by the Bacillus diphtheriæ of Klebs-Loeffler, and by the toxin which it produces. The disease is characterized first by the formation of a local fibrinous exudate upon the mucous membranes, especially of the throat and upper respiratory passages, and second, by constitutional symptoms caused by the absorption of the toxin from the local lesion.

THE ETIOLOGY OF DIPHTHERIA

Bacteriology.—The Corynebacterium diphtheriæ was discovered and described by Klebs in 1883, but Loeffler in 1884 was the first one to grow the pure culture and to identify it as the bacteriological cause of diphtheria. The bacilli are notably variable in shape and size, being either straight or slightly curved, and with irregularly stained granular bodies at one or both ends, or sometimes between. They are apt to lie in groups of parallel organisms. They are Gram-positive, non-motile and do not produce spores. The Klebs-Loeffler bacilli are killed in ten minutes at 60° C., and almost instantly at 100° C., and have little power of resistance to

[1] Sixteenth Annual Report (for 1853) of the Registrar General, Great Britain. P. 83 of Appendix. Date of publication, 1856.

antiseptics. On the other hand, cold kills slowly, and the bacilli may survive for weeks in ice. In milk and water they also survive for long periods. Dried membrane may contain toxic living bacilli for several months, but when finely distributed by a spray the bacilli die out in two days or less in an ordinary sun-lit room.

The sulfonamides have no effect on the diphtheria bacillus or its toxin. Most strains of diphtheria bacilli are sensitive to penicillin as judged by *in vitro* tests, and similar effectiveness is displayed by the tetracycline drugs. However, attempts to use antibiotics to protect guinea pigs against infection with *C. diphtheriæ* have yielded equivocal results.



FIG 5.—One of the very characteristic forms of diphtheria bacilli from blood-serum cultures, showing clubbed ends and irregular stain × 1100 diameters Stain, methylene blue (Park and Williams, Pathogenic Microorganisms.)

Identification.—Diphtheria bacilli can often be identified in immediate smears prepared with Neisser's or with Ponder's stain, which differentiate the metachromatic granules from the body of the bacilli. They are Gram-positive. A much more certain method of identifying the bacilli is to culture a suspected diphtheritic area onto Loeffler's serum agar slants (a culture medium consisting of a mixture of dextrose, bouillon, and blood serum).

In taking cultures, sterilized cotton swabs twisted on applicators are applied under the margins and on the surface

of the diphtheritic membrane. In laryngeal cases it is not sufficient to culture the pharynx unless there is false membrane visible there, but it is necessary to take a culture direct from the involved area in the larynx. In culturing healthy people or convalescents from the disease, cultures should be taken not only from the pharyngeal wall, but especially from the tonsillar crypts and from the nasal passages The culture swab is passed gently up and down over the surface of a Loeffler serum agar culture tube, and the tube is placed in an incubator at 37° C The culture is incubated from eight to twenty-four hours, and then smears are made of the colonies found on the surface of the culture medium The smears are stained with Loeffler's methylene blue or with Ponder's stain Negative cultures do not rule out the presence of the disease, nor do positive cultures necessitate it In fact, 20 per cent of the initial cultures taken in cases of clinical diphtheria are negative, and healthy carriers of diphtheria bacilli are common

Potassium tellurite in a blood agar medium has been popular for the isolation of diphtheria bacilli The tellurite, if used in suitable proportions, impedes the growth of the oral flora without injuring the diphtheria bacilli which grow in readily visible black colonies

A so-called rapid method of identifying diphtheria bacilli has also been developed (Solé, Brahdy *et al.*). Special sterile swabs are impregnated with sterile undiluted unheated horse serum to which no preservative has been added, and then are lightly flamed to obtain surface coagulation These swabs are used for taking the culture in the routine manner, and also are used as the culture medium, being incubated two to four hours in an ordinary sterile glass tube in an incubator or a vest pocket Smear preparations are made direct from the swabs, and on examination these have revealed a higher percentage of accurate results and at a much earlier time than the older Loeffler method.

The Toxin.—The diphtheria bacillus when growing in the throat or in artificial culture media produces a soluble toxin,

which, when injected in sufficient doses into susceptible animals, causes death. The toxin is unstable, aging, light, heat, and exposure all causing deterioration, and a temperature of 75° C. for ten minutes causing destruction. Strains of true diphteria bacilli, although culturally alike, may possess widely varying amounts of virulence, that is, they may produce toxin in great quantity, or none. Virulent and avirulent diphtheria bacilli themselves are differentiated by so-called virulence tests. A few drops of a suspension in broth of the diphtheria bacilli in question are injected into the skin of each of two guinea-pigs, one of which is also given 1500 units of diphtheria antitoxin subcutaneously. Virulent or toxin-producing bacilli will cause a local area of inflammation with necrosis in forty-eight to seventy-two hours in the animal not protected by the antitoxin. With the use of a potassium tellurite medium for the initial culture the time for the toxicity test may be shortened from about a week to four or five days (Dolgopol and Markus).

It has recently been shown that avirulent strains of C. diphtheriæ may become virulent in the presence of a bacteriophage. These C. diphtheriæ bacteriophages are type-specific. They lyse the great majority of the organisms in the susceptible culture, only those mutants remaining intact which are resistant to the phage. This phenomenon occurs both with virulent C. diphtheriæ strains, and with non-virulent ones (i.e., those which do not produce toxin). The bacterial cells which survive exposure of an avirulent culture to certain bacteriophage emerge as virulent. This means that under stimulus of the bacteriophage, organisms originally incapable of producing toxin acquire the property of doing so. Thus they change from avirulent to virulent organisms. Furthermore, this alteration is permanent, being present in subsequent generations. It has been postulated that this phenomenon may have practical importance. A considerable portion of diphtheria bacilli isolated from carriers (healthy or otherwise) have bacteriophages. Should a patient be infected with both a phage-carrying strain and a

strain susceptible to the phage, a change from avirulence to virulence might occur It is not known how frequently such a coincidence occurs, but it has been suggested that bacteriophages may be the principal agents inducing the avirulent to virulent variation in C. diphtheriæ These observations may account for some hitherto unexplained discrepancies in the results of virulence tests which are encountered in studying diphtheria patients.

Three types of diphtheria bacilli, B. diphtheriæ gravis, B. diphtheriæ mitis, and an intermediate type, are recognized particularly in Europe with several cultural differences *involving the fermentation of starch and glycogen. However*, any type may cause mild or severe diphtheria, or be avirulent (Frobischer), and the toxins of different virulent diphtheria bacilli appear to be identical for all strains, so that the antitoxin produced by the immunization of horses with a single toxin is capable of neutralizing all diphtheria toxins (Povitzky *et al*) The Klebs-Loeffler bacillus becomes exalted in its virulence in an environment containing products of streptococci, and malignant cases are often instances of a double infection due to diphtheria bacilli and streptococci.

THE EPIDEMIOLOGY OF DIPHTHERIA

The disease is endemic the world over, especially in the temperate zone, the incidence being apt to show increases in most northern countries from October to May. Children, particularly between the ages of one and five years, are especially susceptible—girls slightly more than boys—but the mortality in boys is slightly higher because of their greater tendency to have the laryngeal form of the disease In recent years an increasing proportion of cases has occurred in adults because the incidence in children has been markedly reduced by *widespread immunization. In fact, in the severe* epidemic in Halifax in 1940 and 1941, 69.2 per cent of the cases were in persons over fifteen years of age. In general,

climatic and social conditions are of greater importance than any racial influence. (Also see Immunity, page 126.)

During World War II, the leading epidemic disease on the European continent both as to morbidity and mortality was diphtheria. Estimates indicate at least a million cases in 1943 on that continent outside of Soviet Russia with a mortality exceeding 5 per cent. The increase began in Germany prior to the war and spread to the countries that were overrun by the Nazis so that, for example, the rates per 100,000 population from 1939 to 1943 jumped in the Netherlands from 16.6 to 638.9 and in Norway from 1.8 to 752.8. By contrast there was a drop in Britain from 114 to 84.

Abnormal conditions such as chronic infection of the respiratory tract, diseased tonsils and adenoids, and convalescence from measles and scarlet fever, are important factors. Infection is usually due to contact with cases of the disease or with healthy carriers of virulent organisms, but milk-borne epidemics have been reported in considerable number and cats have been shown to act as carriers of virulent bacilli for from one to four days after exposure, through contamination *of the rhinopharynx and fur.*

As stated, enlarged or diseased tonsils apparently act as a contributing factor towards the contraction of diphtheria and they also serve as a nesting place for diphtheria bacilli in chronic carriers. Thus tonsillectomy may tend to produce immunity in a considerable proportion of children, as well as to clear up a carrier condition. Before a child's tonsils are removed, he should be known either to be immune to diphtheria—*i.e.*, to be Schick-negative—or to be free of virulent diphtheria bacilli. Diphtheria superimposed on the raw field of a tonsillectomy is usually very malignant. (See Fig. 12, page 110.)

THE PATHOLOGY OF DIPHTHERIA

Two factors are necessary for the production of the disease, the presence of the specific bacillus, and the existence in

the host of susceptibility to the disease Ordinarily, diphtheria bacilli attack only epithelial tissue, usually a mucous membrane. After the surface seeding, the bacteria grow in the normal cellular detritus and mucin Toxin is produced which, unless counteracted by the host's antitoxin or by antitoxin introduced during treatment, causes necrosis in the



[illegible] Diphtheria of the trachea. Photomicrograph of [illegible]

underlying mucous membrane, thus furnishing more soil for further growth of the bacilli and in turn for production of more toxin. The diphtheria bacilli are usually found only in the necrotic material, and do not ordinarily invade living tissue; but, either just before or after a patient's death, the bacilli occasionally enter the blood stream and can be cul-

tured at autopsy from the blood of the heart and spleen The toxin, however, is readily absorbed. The characteristic lesions of diphtheria are therefore both local and systemic or general The former are due to the action of the diphtheria bacilli and especially their toxin at the site of the infection, and the latter to the toxin alone which is absorbed through the blood and lymph streams.



FIG 7.—Diphtheria of the lung Photomicrograph of a section from the lung of a case of diphtheria of the entire upper respiratory tract showing diphtheritic membrane on the wall of a bronchiole (a) and extending out into the alveoli (b)

The Local Lesions.—These are characterized by degenerative and necrotic changes in the epithelial cells, and by an abundant serous and fibrinous exudation from the blood vessels into the underlying tissues and on the denuded surface As a result of coagulation of the serum there is formed on the surface one or more small patches of a thin, closely adherent, pale, so-called false or pseudo-membrane which soon spreads, becomes confluent, thick, usually tough

but occasionally friable, and varies in color from white or yellowish-white to gray, and even quite dark—depending on the quantity of blood in the pseudo-membrane. On microscopic section this false membrane is found to be laminated, dense, and fibrinous, and lying directly over the denuded surface of the mucosa since the epithelium has been destroyed. It is composed of bacilli, fibrin, degenerative and necrotic epithelial cells, and white and red blood cells, all in varying proportions, depending on the age of the membrane and somewhat on its location The subjacent tissue is deeply congested and occasionally markedly edematous and hemorrhagic, and there is an outpouring of fibrin into the soft tissues If the membrane is forcibly removed from the tonsils the underlying tissue bleeds readily, but elsewhere as in the larynx and trachea, the basement membrane remains intact and typically there is no ulceration, although the surface mucosa or epithelium is destroyed. The diphtheritic pseudo-membrane is usually found on the tonsils, soft palate, uvula, and nasopharyngeal wall, also at times in the nose, larynx, trachea (Fig. 6), and even the bronchi. The local lesion of the larynx is of special importance because the narrow respiratory passage between the vocal cords may be readily obstructed by congestion and edema of the mucosa, and by the false membrane, giving rise to respiratory difficulty. A diphtheritic fibrinous exudate extending from the bronchi out into the alveoli of the lungs has also been demonstrated microscopically (Fig 7) Thus the diphtheria bacillus seems to attack mainly the respiratory mucous membranes proper, infection of the esophagus and of the front of the mouth being rare. Infections of other mucous membranes such as those of the eye and vagina, do occur, though uncommonly, and middle ears, wounds, and burned areas are also occasionally involved.

The Systemic or Secondary Lesions.—These are characterized by toxic degeneration, first of the viscera (particularly of the heart muscle and less notably of the liver, kidneys, and

lymphoid organs), and second of the cranial and peripheral motor nerves.

The heart lesion is a primary toxic hyaline degeneration of the muscle fibers with edema and congestion of the interstitial tissue. A cellular infiltration of the interstices with

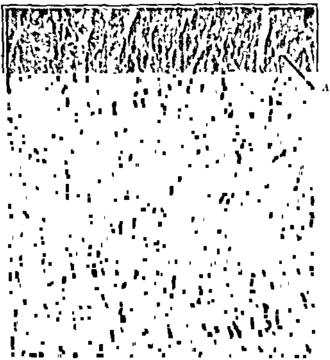


FIG 8.—Diphtheria. Myocarditis. *A*—fragmentation of muscle fibers, *B*—Zenker's degeneration, *C*—interstitial cellular infiltration (From the collection of Dr. Vera B. Dolgopol.)

predominantly mononuclear cells occurs around the degenerated muscle, later followed by regeneration of the muscle or by the formation of multiple scars. The conductive system is also sometimes involved in a similar way. If

scarring is not extensive, regeneration of the muscle may satisfactorily replace the damaged tissue

In any case of diphtheria the toxin acts upon all tissues, causing degenerative reactions, and the involvement of highly specialized tissues such as nerves and heart muscles causes symptoms earlier than equivalent lesions in other and less specialized tissues As the toxemia progresses, the degenerative process in heart muscle, conducting system, vagus nerve, vasomotor centers, and arterial muscle fibers increases until any one or more of these becomes incapable of maintaining its burden, and symptoms of circulatory failure develop. Ordinarily the heart muscle fibers fail first, and irregularities of pulse appear, the liver becomes engorged, and general symptoms of myocardial insufficiency are present If the action of the toxin progresses, however, the failure of any one or any combination of these systems may become so great as to be incompatible with life. If, however, the toxemia is not overwhelming, the symptoms begin to abate, and the patient starts to convalesce. Regeneration of heart muscle may proceed unimpeded and the patient may make a complete recovery with no resulting cardiac weakness. On the other hand, the damage to the myocardium may be so great that cardiac failure results Death from diphtheritic myocarditis may occur as early as the third day of the disease, or may be delayed for five or six weeks

In the lymphoid organs, there is a generalized hyperplasia with toxic degeneration of the follicles going on to necrosis and affecting tonsils, lymph nodes, and spleen The liver may show a toxic necrosis of the parenchyma, mainly in the centers of the lobules, and there is apparently a disturbance in the storage of glycogen, hence the benefits obtained from the *intravenous* administration of glucose solutions in the treatment of toxic cases.

The kidney changes are limited to the tubules and vary from simple degeneration to necrosis of tubular epithelium.

The action of the toxin on the central nervous system seems

to be of two types. (1) There is an early toxic effect said to be due to passage of the toxin up the perineural lymph stream and perhaps up the nerves themselves, resulting in the first week or two in a comparatively local paralysis, due to the action of the toxin on the peripheral nerves, particularly the cranial nerves Fatty degeneration is occasionally demonstrable in the myelin sheaths. (2) The toxin may also pass to the blood stream and therein to the central nervous system, and so cause widespread degenerative changes in the substance of the cord and brain as well as in the nerve fibers Thus there is found a later, more generalized paralysis which may occur even six to eight weeks after the onset of the disease

Diphtheria toxin produces hemorrhage and necrotic lesions in the cortex and medulla of the adrenal glands of guinea pigs Lesions in the adrenal are also found in man. Rich found focal hemorrhage and necrosis of the cells of the adrenal cortex in 19 of the 40 successive fatal cases of diphtheria which he examined between 1946 and 1949 The lesions in some instances were as extensive as those encountered in overwhelming meningococcic infection.

There is nothing characteristic of the blood count in diphtheria The extent of the leukocytosis varies as the severity of the infection Diphtheria does not significantly affect the tuberculin skin reaction as do measles and scarlet fever

THE INCUBATION PERIOD OF DIPHTHERIA

The incubation period of diphtheria is one to seven days, usually two to four The constitutional disturbances, such as fever and other subjective symptoms, usually do not appear until the local manifestations have reached a sufficient degree of intensity

THE CLINICAL MANIFESTATIONS OF DIPHTHERIA

For purposes of study, the disease is best classified according to the location of the diphtheritic membrane, and thus

scarring is not extensive, regeneration of the muscle may satisfactorily replace the damaged tissue

In any case of diphtheria the toxin acts upon all tissues, causing degenerative reactions, and the involvement of highly specialized tissues such as nerves and heart muscles causes symptoms earlier than equivalent lesions in other and less specialized tissues As the toxemia progresses, the degenerative process in heart muscle, conducting system, vagus nerve, vasomotor centers, and arterial muscle fibers increases until any one or more of these becomes incapable of maintaining its burden, and symptoms of circulatory failure develop Ordinarily the heart muscle fibers fail first, and irregularities of pulse appear, the liver becomes engorged, and general symptoms of myocardial insufficiency are present If the action of the toxin progresses, however, the failure of any one or any combination of these systems may become so great as to be incompatible with life If, however, the toxemia is not overwhelming, the symptoms begin to abate, and the patient starts to convalesce. Regeneration of heart muscle may proceed unimpeded and the patient may make a complete recovery with no resulting cardiac weakness On the other hand, the damage to the myocardium may be so great that cardiac failure results Death from diphtheritic myocarditis may occur as early as the third day of the disease, or may be delayed for five or six weeks

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The kidney changes are limited to the tubules and vary from simple degeneration to necrosis of tubular epithelium.

The action of the toxin on the central nervous system seems

II. Faucial or Pharyngeal Diphtheria

The symptoms and signs vary markedly according to the severity of the disease. Characteristically there is a sudden onset of mild pain in the throat, with fever gradually increasing to a maximum of 101° to 102° F. in uncomplicated diphtheria though commonly remaining around 100° Malaise,

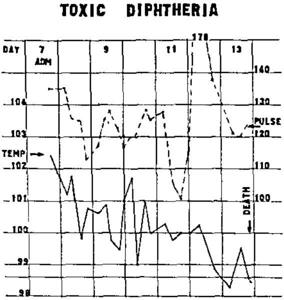


FIG 9 —Showing a fatal case of nasal and faucial diphtheria in a baby, aged seventeen months, who received no antitoxin until the seventh day of illness

prostration, and an increase in the pulse-rate are all quite out of proportion to the amount of fever, and headache may be quite troublesome The throat pain is usually not as marked as in tonsillitis—in fact, a child may seem merely sick and not complain of the throat.

into the following types: (1) nasal; (2) faucial or pharyngeal, (3) laryngeal, or diphtheritic croup, (4) combinations thereof, (5) diphtheria elsewhere, as of the eye, ear, vagina, wounds, etc

For all forms of diphtheria, diagnosis is aided by the appearance of the membrane, the reaction to antitoxin, the previous reaction of the Schick test, and the cultural findings. Examination of the blood in diphtheria gives little if any aid in diagnosis

I. Nasal Diphtheria

The onset is customarily like that of a simple head cold with little or no fever and malaise There is usually and characteristically a "sero-sanguinous nasal discharge that excoriates the upper lip." The infection may be unilateral but is more commonly bilateral. After the discharge has been cleaned away, a diphtheritic pseudomembrane may often be seen on the mucous membrane of the nose Hemorrhage from the nose may be quite severe, there may be constant oozing, or there may be merely a tinge of blood in the nasal discharge Since absorption of toxin from the anterior part of the nose is poor, constitutional manifestations are usually slight when the nose only is involved When the nose involvement is part of a more extensive diphtheria involving the nasopharynx and pharynx generally, the patient as a rule is very ill. Moderate cases of nasal diphtheria are uncommon.

If untreated with antitoxin, simple nasal diphtheria may run on for many days despite the use of local antiseptics. The administration of antitoxin cures the condition promptly. This form of diphtheria is of great importance because of the frequency with which the correct diagnosis is overlooked for some days, the patient continuing to be a potent source of infection to others.

Complications of Nasal Diphtheria.—With the exception of cervical adenitis, which is usually marked in the extensive cases, complications of simple nasal diphtheria are unusual, but occasionally sinusitis and otitis media are found

PLATE II



Diphtheria of the pharynx showing edema and congestion of the pharyngeal membranes with extensive diphtheritic exudate on each side of the pharynx and on the uvula The tongue is markedly coated (Reproduced by courtesy of Parke, Davis & Company, from "Therapeutic Notes")

In the pharynx there is at first a moderate redness of the tonsils and pillars. A semi-opaque whitish exudate appears in one or more places and quickly becomes more extensive, *thicker, and more confluent, spreading from the tonsil onto* the mucous membrane of the soft palate. False membrane on the tip or posterior surface of the uvula is especially suggestive of diphtheria. The membrane may bridge the soft palate in two to four days and in extreme cases may extend from the anterior nares through the nose, pharynx, and



Fig. 10. Cervical adenitis or 'bull neck' in diphtheria

trachea to the bronchi. The membrane varies in color according to the amount of blood in it. It is usually a dirty grayish-white but may be milky-colored, gray, or almost black. In the early stages it clings tenaciously to the underlying mucous membrane, especially to the tonsils, and on forcible removal leaves a bleeding surface. When older or after the administration of antitoxin, it curls up at the edges and disintegrates or becomes detached in large pieces.

If untreated with antitoxin, the course of the disease may go on to death in six to ten days, or the membrane may disappear in eight to ten *days and the patient go on to a long* and stormy convalescence, in which marked evidences of the

effect of the toxin on the heart and nerves are usually found But following the administration of a sufficient dose of diphtheria antitoxin, the membrane ceases to spread and within twenty-four hours is appreciably smaller in extent and disappears in two or three days. The fever usually returns to normal nearly as quickly and in uncomplicated cases the constitutional symptoms are soon gone.

A so-called characteristic sweetish odor of diphtheria has been described This is best obtained in cases of extensive exudate and is probably the odor of sepsis rather than that specifically of diphtheria

Complications of Faucial Diphtheria —Complications of faucial diphtheria due to secondary infection with extension of the inflammation include otitis media, cervical lymphadenitis or "bull neck," and peritonsillar abscess or quinsy Complications due to toxemia are principally myocarditis, neuritis, and also nephritis (See page 111)

III. Laryngeal Diphtheria or Diphtheritic Croup

Laryngeal diphtheria occurs in about one-fourth of all cases of diphtheria (261 in 1009) The involvement is in the larynx alone in about one-fourth of these instances but is part of a more general diphtheritic infection in the other three-fourths Laryngeal diphtheria is most common in young children from one to four years of age (77 per cent of the cases), and affects boys (56 per cent) slightly more frequently than girls

Diphtheritic membrane in the larynx is usually thinner than that found in the fauces, and is more easily detachable, especially when three or four days old However, because it rapidly produces mechanical obstruction to breathing, diphtheria of the larynx is always serious As elsewhere, the infection causes congestion and edema, which in this type of diphtheria involve at times the entire glottis This swelling of the tissues, together with the thickening pseudomembrane and a purulent exudation, narrows and constricts the lumen of this part of the air passages Because of increas-

Restlessness is usually marked as the unfortunate child fights for air, and only aggravates the trouble. At times there is a distressing spasm of the laryngeal muscles. Cyanosis from improper aëration of the blood becomes progressively more marked, or an ashen pallor may appear around the mouth. Without antitoxin and surgical intervention, exhaustion appears, the child becomes comatose, and death may occur as early as the third day of the disease.

After antitoxin has been given and has become effective, cases of diphtheritic laryngitis may gradually recover without surgical assistance The membrane ceases to spread, becomes loose, and is coughed up, and the signs of respiratory obstruction gradually disappear. Progress may be greatly helped by aspiration of the mucus and membranous exudate from the larynx (See Treatment.) When intubation (or tracheotomy) has been done, giving immediate relief to the respiratory obstruction, the exhausted little patient usually falls into a deep sleep Then a day or so later when the membrane loosens there is a marked tendency to cough up the tube with the membrane Four or five days after intubation the temperature usually has returned to normal, and the intubation tube may be removed The child then gradually regains his voice and strength and makes a perfect recovery

The Complications and Sequelæ of Laryngeal Diphtheria.—1 *Bronchopneumonia* —The onset of bronchopneumonia is accompanied by a rise in the temperature, pulse, and respiration-rates with increasing prostration and toxicity Usually the diagnosis can be made from the temperature chart and the general appearance of the child The customary physical signs of bronchopneumonia may or may not be found, but the diagnosis is readily confirmed by roentgen-ray examination The presence of an intubation tube in the larynx causes chest signs which increase the difficulty of diagnosis of lung conditions

2 *Atelectasis* —In severe cases, especially of laryngo-tracheal diphtheria, patchy areas of atelectasis, particularly

ing difficulty in breathing, the ensuing strain on the heart, and the liability to a secondary bronchopneumonia, cases of laryngeal diphtheria become serious much more rapidly and are more frequently fatal than other types of diphtheria. Fever is rather higher in laryngeal diphtheria than in faucial or nasal diphtheria, and usually lasts longer after the administration of antitoxin. A temperature of 103° to 104° F. for three or four days is not unusual. On the other hand, diphtheritic involvement of the larynx alone is less liable to be accompanied by the absorption of toxin, or to be followed by paralyses than are the other common forms of diphtheria.

Diphtheritic laryngitis begins with a mild fever, hoarseness (due to the customary involvement of the vocal cords), an occasional tight, dry cough, and presently some evidence of difficulty in breathing. The symptoms progress steadily without remission, except for slight improvement when the child is soothed and quieted as compared to conditions when the child is frightened and worried Within forty-eight hours of the onset the child may present an appearance of being critically ill, the face being anxious and pale, the head slightly drawn back, and the breathing increased in rate, range, and effort The voice may be merely hoarse or it may be entirely lost for the duration of the disease. The cough may be frequent, and is usually dry, hacking, and characteristically croupy in character. In pushing and pulling air past the diphtheritic obstruction the child may be observed to be using all the accessory muscles of respiration, and retractions appear above the sternum in the soft tissues of the neck and immediately below the sternum in the epigastrium. The younger the child, the deeper are the retractions These are due to the negative pressure resulting from the forcible lifting of the chest wall, the lungs lagging behind, being unable to expand rapidly In severe cases there may even be a downward movement of the larynx with each inspiration With the marked dyspnea (literally difficult breathing), there is often an inspiratory stridor, and examination of the lungs shows diminution or loss of the vesicular murmur.

of the skin. Such infections occur either with or without diphtheria of the upper respiratory mucous membranes, and are often characterized by indolent membranous infections which resist the usual remedies but clear up quickly after the intramuscular or intravenous administration of antitoxin. These infections are often diagnosed correctly *only when subsequent cases of diphtheria have occurred in* their vicinity and the source of these new cases has been sought

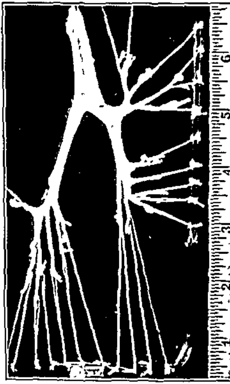


FIG 11 —Diphtheritic membrane removed after death through a tracheotomy incision in a six-year-old boy It evidently extended from the larynx past the bifurcation and on the left side into both lobes and to the lesser bronchi. (From Tull, Jour Am Med Assn , 104, 1967, June 1, 1935)

in the peripheral areas of the lungs may appear on roentgen-ray examination This condition has been thought due to incomplete aeration, in turn caused by diminished pulmonary expansion, and occurs without associated clinical manifestations

3. *Acute Mechanical Respiratory Obstruction.*—Acute mechanical respiratory obstruction may result from the local diphtheritic process, causing death from heart failure or asphyxia unless surgical intervention is resorted to or unless the benefit of diphtheria antitoxin is obtained before this stage is reached

4 *Chronic Laryngeal Obstruction* —Chronic laryngeal obstruction is often a sequel to the acute inflammation, or to injury resulting from operative procedures (See Treatment, page 143.)

IV. Multiple Diphtheria

The diphtheritic process may involve the mucous membrane of more than one general area, such as the pharynx, the larynx, and the trachea In fact pseudomembranes have been found at autopsy, extending from the nostrils through the pharynx, the larynx, and the trachea down to the lesser bronchi, and microscopic sections have revealed diphtheritic involvement even of the bronchioles and alveoli

These multiple or extensive cases of diphtheria are almost invariably in patients with little immunity or resistance, and are characterized from the beginning of the illness by the severity of the disease and the overwhelming toxicity of the infection Secondary infections and other complications are common, and a massive dose of antitoxin at the earliest opportunity is essential if the patient is to be saved.

V. Diphtheritic Infection Elsewhere

Diphtheritic infection with membrane formation has been reported also in the eye, the external auditory canal, and the vagina. It has been found on wound surfaces and in ulcers

of the skin Such infections occur either with or without diphtheria of the upper respiratory mucous membranes, and are often characterized by indolent membranous infections which resist the usual remedies but clear up quickly after the intramuscular or intravenous administration of antitoxin. These infections are often diagnosed correctly only when subsequent cases of diphtheria have occurred in their vicinity and the source of these new cases has been sought.

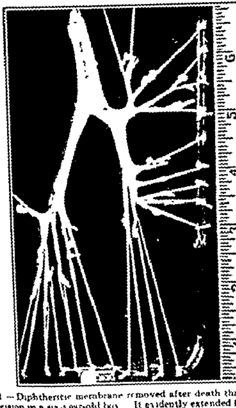


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In general, the involvement in diphtheria varies considerably in degree, depending on the host's amount of circulating antitoxin and his ability to produce more, and on the virulence and number of the attacking bacteria The disease may therefore be classified as *simple*, *toxic*, or *septic* in type Simple cases are those in which the local and general manifestations are mild Toxic cases are those in which the manifestations due to the absorption of toxin (such as pros-

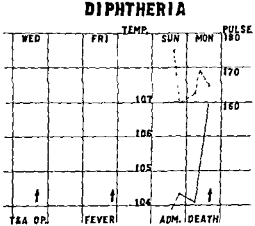


FIG 12 —Showing a highly toxic and rapidly fatal case of faucial diphtheria in a child, aged six years The onset was two days after a tonsillectomy.

tration, fever, impaired heart action, and other evidences of toxemia) are marked Septic cases are those in which the local infection is severe, the membrane is extensive, the regional lymph nodes are swollen and there are evidences of extension of the infection (or of a secondary infection) to the adjacent organs, such as the ears or the sinuses.

Toxic Diphtheria.—*Certain cases of diphtheria, particularly when the infection involves the nasopharynx, are accompanied by evidences of a high degree of toxemia.* The patient appears markedly prostrated and apathetic, the skin

is pale, smooth and waxy in appearance Petechiae and ecchymotic areas may appear, indicating a grave prognosis Signs of myocardial involvement are present, and these may progress until evidences of cardiac decompensation and circulatory collapse are apparent. The patient becomes weaker blood pressure falls, periods of delirium occur, and coma and death may follow

Septic Diphtheria.—Cases are occasionally seen, particularly of faucial diphtheria, where the local reaction to the infection is unusually severe Secondary infection with streptococci aggravating the virulence of the diphtheria toxin is often an underlying factor in these septic cases The membrane is unusually extensive and piled up, and is especially foul in odor. The underlying tissues are markedly swollen and inflamed, as are the cervical lymph nodes together with the adjacent tissues of the neck, with the result that the whole neck is so markedly enlarged as to warrant the name "bull-neck" There is often an extension to the middle-ear spaces and hemorrhages from the nose or throat are not uncommon The temperature is septic in type with marked daily fluctuations, and the pulse is usually rapid and thready The prognosis is bad, especially since the patients are apt to be not only septic but also very toxic

THE GENERAL COMPLICATIONS OF DIPHTHERIA

In general the complications of diphtheria are due to a secondary infection, usually with a streptococcus, or to extension of the diphtheritic infection to the lungs or ears, or to the effect of the absorbed toxin on the kidneys, heart or central nervous system

1 *Albuminuria* to some extent is apt to occur in nearly every case, clearing up with the fever Sufficient involvement of the kidneys to be termed a clinical nephritis may be recognized clinically in as many as 15 per cent of all cases, and in some series of autopsies more or less involvement of the kidneys has been found in the majority of instances

2 *Cervical Adenitis.*—When moderate in amount this can be considered part of diphtheria and due to the absorption of toxin, but when extensive it is usually due to a secondary infection. The swelling may be extreme but breaking down of the lymph nodes with abscess formation is comparatively unusual since the patient either dies first of oxemia or responds to proper treatment.

3 *Myocarditis* —Myocarditis is a very frequent complication of diphtheria, and is by *far the most common cause of* death in this disease When careful daily physical examinations and frequent electrocardiographic records are made, evidence of myocarditis is found in 50 per cent of patients with diphtheria.

In general, the more severe the diphtheritic infection the more likely is the occurrence of myocarditis, and the more serious it is likely to be. Patients with extensive membrane formation, severe cervical adenitis, and edema of the neck (bull-neck), nearly always develop myocarditis Nearly 30 per cent of such patients succumb with symptoms of circulatory *failure* *As a rule, patients who have gone undiagnosed* and untreated with diphtheria antitoxin for a long period are more liable to suffer cardiac damage than are those treated early. This difference may be due to delay in instituting bed rest as well as to delay in antitoxin therapy

Signs of myocarditis may be apparent as early as the second day of the disease, or they may not be detected until three to six weeks after onset In general, the earlier the evidence of myocarditis is obtained the more serious is it likely to be. In our experience with 350 successive patients with diphtheritic heart disease, evidence of myocarditis in all fatal cases was *obtained before the twelfth day of diphtheria*

Usually, the first physical sign of cardiac involvement is a decrease in the volume of the first heart sound at the apex. This change may be very slight at first, but to an experienced observer it is usually quite definite As the myocardial damage progresses, the first heart sound becomes progressively fainter, until it is barely audible. Sometimes a blowing

systolic apical murmur is heard, and cardiac enlargement may be detected by physical examination and by roentgen-ray pictures Various arrhythmias may occur, including premature contractions, dropped beats, complete heart block, and terminally, ventricular tachycardia and fibrillation

Abnormal electrocardiographic findings are encountered in approximately 50 per cent of all patients with diphtheria if frequent records are obtained. Some of these changes are of minor significance, especially if they are not accompanied by clinical signs of myocarditis For example, elevation of the S-T segment is frequently seen without any other evidence of heart disease However, such abnormalities as prolongation of the P-R interval, more advanced forms of heart block, contractions arising from ectopic foci and ventricular tachycardia may be present and must be considered to indicate more serious degrees of myocardial damage Complete auriculo-ventricular dissociation, while of very grave significance, is not always fatal in diphtheritic myocarditis as has frequently been stated Six of twelve patients with this condition treated by us recovered completely In general the electrocardiographic and clinical findings go hand in hand However, severe evidence of myocarditis occasionally is present on the electrocardiogram when no clinical evidence of myocarditis is present, and sometimes the reverse is true

The *circulatory failure* caused by diphtheria is very complex In most instances it is clear that damage to the myocardium is the cause of the circulatory collapse In other cases peripheral circulatory factors also seem to be involved, and a shock-like state resembling that seen in acute adrenal insufficiency is encountered.

Circulatory failure may occur during the first three or four days of the disease, or as late as six weeks after onset In our experience the former is much more common There is no doubt, however, that the so-called "late circulatory failure" is by no means an extreme rarity It may occur after the height of the disease is past, when the patient seems well on the way to recovery (Fig 13)

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effort, such as sitting up in a chair or getting out of bed to walk across the room.

The ultimate prognosis of myocarditis in diphtheria, if the patient survives, is excellent, recovery usually being complete

4. *Bronchopneumonia* is especially common with laryngeal diphtheria but is also frequently met in septic faucial diphtheria. Where the diphtheritic involvement extends down the trachea to the bronchi, bronchopneumonia is probably always present, and may be due to the diphtheria bacillus or more commonly to streptococci. Because the most common form of bronchopneumonia in diphtheria is that in which there are disseminated foci of infection scattered through both lungs, physical signs of the disease other than the persistent high fever, rapid pulse, and frequent shallow respirations may be difficult to detect. A roentgen-ray examination might reveal the presence of this complication but these patients are ordinarily too sick to be disturbed for the taking of the roentgen-ray picture In many cases, however, the physical signs of extensive consolidation are readily detected

5 *Diphtheritic Neuritis or Paralysis*—This is frequently met particularly in those cases in which the administration of antitoxin was as late as the fourth day of the disease In large series of cases the incidence of paralysis is from 7 to 20 per cent. There are two main types: an early local, and a late general or multiple paralysis To cause the former, there is absorption of the toxin from the pharynx to the central nervous system by the perineural lymphatics with resulting toxic degeneration of the peripheral motor neurones, the cranial nerves being those particularly affected Clinically the commonest paralyses are of the muscles of the soft palate and of the ciliary muscles of the eye, the latter due to involvement of certain fibers of the oculomotor nerve, but the extrinsic eye muscles are rarely involved except for very occasional strabismus due to involvement of the abducens nerve. Temporary weakness of the facial nerve has also been reported though it is rare, but difficulty in swallowing

The circulatory failure of diphtheria is usually ushered in by a change for the worse in the heart sounds, which become faint and irregular. The electrocardiogram may show ectopic beats, various degrees of heart block, and ventricular tachycardia. The patient is restless and anxious and complains of abdominal pain Vomiting is common. The liver is usually enlarged, and tender, and rales may be heard over the bases of the lungs In addition to these evidences of myocardial

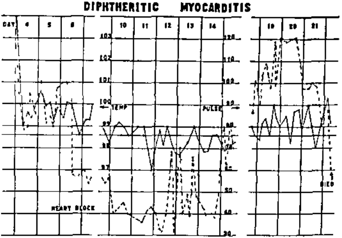


FIG. 13 —A fatal case of toxic faucial diphtheria in a man, aged twenty-two years, showing an early heart-block, followed by temporary improvement, and then sudden death on the twenty-second day of illness, due to the late type of myocarditis

failure, certain shock-like symptoms may be present. The skin becomes pale or grayish, blood pressure falls, and blood volume is diminished The patient may become delirious, lapse into unconsciousness and die within an hour or two, or on rare occasions, gradual improvement and recovery may occur.

Instances have been reported when, during an apparently well established early convalescence, an entirely unexpected death may suddenly occur after some comparatively trivial

Formerly about 5 per cent of hospital cases of diphtheria developed acute purulent otitis media, and of these about 10 per cent went on to mastoiditis, but use of the antibiotics has materially lowered these percentages

7. *Secondary Anemia.*—Secondary anemia is almost always *present in diphtheria, occasionally to a marked degree* Early administration of antitoxin helps to minimize it

8 *Other complications* of acute diphtheria may be general sepsis, peritonsillar abscess, sinusitis, hemorrhage from the mucous membranes especially of the nose, enteritis particularly in infants, and more rarely thrombosis and embolism Diphtheria and scarlet fever occasionally occur together

Death from diphtheria is usually due to toxemia and cardiac involvement but bronchopneumonia, respiratory obstruction, and sepsis are occasional causes

THE DIFFERENTIAL DIAGNOSIS OF DIPHTHERIA

In practice, the diagnosis of diphtheria must be made on clinical grounds because dependable methods for demonstrating C diphtheriæ require incubation of cultures for twelve to eighteen hours A delay of this duration in giving antitoxin may cause serious damage. The laboratory should be used as an auxiliary aid in diagnosis only.

I Nasal Diphtheria

1 *A Simple Cold or Coryza.*—This sometimes can be differentiated only by culture, but nasal diphtheria should be suspected whenever the nasal discharge is blood-tinged, excoriating and protracted, also where a false membrane is visible

2 *A Foreign Body, Such as a Bead, Button or Piece of Paper Inserted by the Child* —Infection is apt to follow and a blood-tinged discharge may be found, but the process is usually unilateral and the foreign body can be found if looked for.

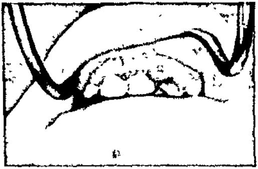
or coughing due to pharyngeal weakness is *not* unusual. Sensory nerves are occasionally also affected, as of the pharynx. Evidence of paralysis is usually first found in blurred speech and regurgitation of fluid through the nose, also in older people in an inability to focus the eyes on near objects, such as book print.

The paralyses usually appear toward the end of the first week or during the second week after the onset of the disease but may be delayed into the fourth week. After the onset of the first evidence of paralysis the crest of the involvement is usually reached within three to five days, following which, if the patient survives the toxemia, there is a gradual convalescence, ending after several months in complete return to normal of all the involved motor nerves

The later the paralysis appears, the more apt it is to be part of a general systemic or hematogenous toxemia, and therefore the more widely distributed are the effects of the toxin on the central nervous system. At any time after the first week and even as late as the ninth week after the onset of the disease when the patient has long since seemed convalescent, weakness may gradually or suddenly appear, spreading even in a few hours' time to involve many different groups of muscles Involvement is usually fairly symmetrical and consists of a paresis or partial weakness rather than a complete paralysis. Involvement of the diaphragm is especially serious, and is due to paralysis of the phrenic nerve It has occurred twenty-six to fifty-six days after the onset of the diphtheria, and may persist for two weeks. Death may occur from suffocation unless the patient can be kept alive by artificial respiration until the crest of the wave has passed and he has begun to recover. In cases where this extensive paralysis occurs early, the toxemia has usually been sufficient to cause also a marked myocarditis, which may prove fatal before failure of the respiratory muscles alone can cause the death.

6. *Otitis Media*.—In hospital practice this occurs less frequently in diphtheria than in scarlet fever or measles.

PLATE III



Acute herpetic stomatitis (Courtesy of Henry M Goldman, M D, from Pfizer Spectrum, appearing in the Jour Am Med Assn)

3. *The Snuffles of Congenital Syphilis.*—While markedly excoriating, this discharge is usually found in early infancy at an age when diphtheria is unusual. Other evidences of a syphilitic infection may be present.

II. Faucial Diphtheria

1. *Simple Follicular Tonsillitis and Quinsy.*—In tonsillitis the fever is usually higher than in diphtheria, 103° F. being fairly common in tonsillitis. Ordinarily the pulse-rate corresponds to the fever; the exudate is patchy, does not spread off the tonsils, and on removal does not leave a bleeding surface. Mild cases of diphtheria may very closely simulate tonsillitis, so that every atypical case of tonsillitis should be cultured. Quinsy, or peritonsillar abscess, may occur both with tonsillitis and with diphtheria and is characterized by severe pain and by displacement of the tonsil toward the mid-line, due to swelling behind and above it. When its presence is simulated in diphtheria, incision greatly increases the gravity of the diphtheria.

2. *Vincent's Angina.*—This may resemble diphtheria clinically, but usually some erosion or ulceration may be found, especially of the tonsils or uvula, and the pseudomembrane is apt to be greenish instead of gray in color, and more friable and of longer duration. The constitutional symptoms are very variable but may be slight. Pain is usually moderate in diphtheria and severe in Vincent's angina. The latter infection does not respond to the administration of diphtheria antitoxin and cultures will be negative for diphtheria. An examination of a stained smear made from the exudate will reveal the characteristic spirilla and fusiform bacilli. The two diseases may co-exist, in which case both the smear and the culture are essential for the laboratory diagnosis of the two infections.

3. *Streptococcus Pharyngitis, as in Scarlet Fever.*—Here the characteristic appearance of the fauces is beefy redness, with greenish mucoid exudate on the tonsils, soft palate, and

posterior pharyngeal wall, characteristically in small flecks, but frequently confluent in vertical patches on the posterior pharyngeal wall. In severe septic cases of scarlet fever the appearance of the pharynx may closely simulate diphtheria. It is to be remembered that although most of the membranous inflammations of the throat seen in measles and scarlet fever, especially at the height of these diseases, are not due to the diphtheria bacillus but rather to a streptococcus or even to the staphylococcus aureus which has been known to cause the formation of diphtheria-like pseudomembranes, nevertheless, the administration of diphtheria antitoxin should be seriously considered if the patient's Schick test is not known to be negative. The presence or absence of diphtheria bacilli may be determined later. Membranous inflammations developing at a later period in measles and scarlet fever, especially in hospitals for contagious diseases, are particularly apt to be due to a diphtheritic infection.

4. *Herpangina Due to Coxsackie Virus Infection.*—In this condition the essential lesion is a vesicle, which becomes denuded, leaving a small ulcer, which may be surrounded by an erythematous zone. The base of the ulcer may be covered by a whitish exudate, but membrane formation is not seen. There may or may not be fever and the course of infection is usually self limited and one to four days in duration.

The lesions of herpangina are characteristically located on the anterior pillars of the fauces; the uvula, palate, and tongue may also be involved but the gingival and buccal mucosa are usually not affected. The ulcers are practically never seen on the mucocutaneous margins. The distribution of these ulcers caused by Coxsackie virus is therefore quite different from the similar lesions of *herpetic stomatitis*, which are usually found on the lips, gums, and anterior portion of the tongue.

5. *The Post-tonsillectomy Throat.*—Especially if damage was done to the faucial pillars in the operation for the removal of the tonsils, the subsequent appearance of the scab covering the field of operation may closely resemble diphtheria.

to spasm of the glottis or to laryngospasm caused by sensitivity to an allergen, or it may represent mild infection of the larynx or epiglottis. Certain cases may seem clearly due to the coexistence of an allergy and a cold. One small girl developed an attack of midnight croup whenever she had a slight cold and then drank sweet milk, for which she had an idiosyncrasy. There is often a history of a previous attack of croup either the previous winter or the preceding night.

2 *Acute Laryngotracheobronchitis, Pseudo-diphtheritic Laryngitis, Streptococcus Laryngitis, or Acute Non-specific Infectious Croup* —In mild cases this may be characterized simply by slight fever, pain, a tight cough, and perhaps a little hoarseness, but in severe cases or when complicating measles or other infectious diseases, the infection may even cause the presence of a diphtheria-like membrane in the larynx, and may reproduce all the findings of laryngeal diphtheria except the presence of the diphtheria bacillus However, there are usually more congestion and edema than in diphtheria, and the exudate is less membranous but may be more gummy and profuse, especially if the infection extends down towards the lungs. The onset is apt to be more sudden, there is a higher fever, and the patient may become prostrated more rapidly, and the vocal cords and with them the voice are apt to be involved as early as in laryngeal diphtheria. Edema above or below the vocal cords is the predominating feature. Spasm of the muscles of the larynx at times causes much distress Streptococci are the usual etiological agents but other bacteria, particularly staphylococci and influenza bacilli, are not uncommon It has been suggested that influenzal and other viruses may be involved also These cases do not respond to diphtheria antitoxin A membrane is present on the tonsils or pharynx in most cases of diphtheritic laryngitis, while none is found in other types of laryngitis However, the pharynx and tonsils are unaffected in about 20 per cent of patients with laryngeal diphtheria For the treatment of these infections, rest, forced fluids, steam inhalations, ipecac, possibly sedatives, and stimulants are indi-

6. *The mucous patches of secondary syphilis* may be mistaken for mild diphtheria. These lesions are usually chronic and painless.

7. *Thrush.*—Thrush occurs especially in early infancy but may simulate a diphtheritic membrane. *However, the patches of thrush usually lie forward in the mouth rather* than in the pharynx and are much whiter and more apt to be discretely scattered than is the diphtheritic membrane.

8. *The oral lesions of the blood dyscrasias*, such as *infectious mononucleosis, agranulocytic angina and the various forms of* leukemia, may be strongly suggestive of diphtheria. This particular point of differentiation is of great importance though often overlooked. Hence, when the lesions are in the *mouth rather than the pharynx, whenever there is a general* glandular enlargement and an enlarged spleen, and whenever the membrane persists after the administration of diphtheria antitoxin, a complete blood study is especially indicated, *including a test for the heterophile antibodies that are found* in infectious mononucleosis In our experience during the past ten years, this latter disease has simulated diphtheria more often than has any other condition.

In general, the presence of patches of adherent grayish or yellowish-gray pseudomembrane on portions of the respiratory mucous membrane other than the tonsils is as a rule indicative of infection with the diphtheria bacillus and should *be treated as such, and antitoxin given without waiting for* confirmation by laboratory data

III. Laryngeal Diphtheria

1. *Spasmodic Laryngitis, False Croup, Allergic Croup, or Midnight Croup.*—This condition at its height may closely simulate a clinical picture of laryngeal diphtheria, often being accompanied by fever and all the clinical symptoms of a laryngeal obstruction, but there is no exudate in the pharynx or larynx. This croup usually has waves of severity being notably more marked by night than by day. It may be due

to spasm of the glottis or to laryngospasm caused by sensitivity to an allergen, or it may represent mild infection of the larynx or epiglottis. Certain cases may seem clearly due to the coexistence of an allergy and a cold. One small girl developed an attack of midnight croup whenever she had a slight cold and then drank sweet milk, for which she had an idiosyncrasy. There is often a history of a previous attack of croup either the previous winter or the preceding night.

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cated, and of course immediate antibiotic therapy in large doses. Oxygen inhalation may prove more beneficial than steam *In carefully selected cases, very gentle intratracheal aspiration with removal of friable exudate may bring marked relief.* When the manifestations of respiratory obstruction are sufficiently severe to require surgical intervention, tracheotomy should be the operation of choice, intubation occasionally being useful but often proving fatal.

3 *Retropharyngeal Abscess.*—The persistence of chains of lymph nodes on each side of the mid-line in the retropharyngeal wall, for about the first two years of life, makes possible in infants this clinical entity of adenitis with abscess formation on one side or the other of the mid-line. There is usually a history of a preceding upper respiratory infection followed by apparent respiratory obstruction, and retraction of the head. When a finger is introduced into the child's pharynx, the diagnosis is made if a soft fluctuating mass is felt in the posterior wall on one side of the mid-line

4. *Bronchopneumonia.*—In infants this may be accompanied by enough dyspnea, hoarseness, and harsh cough to suggest laryngeal diphtheria, even though the larynx be apparently normal

5. *Bronchial Asthma.*—The dyspnea of asthma may suggest laryngeal obstruction, but an expiratory stridor, rather than inspiratory, predominates, and the lungs are filled with high-pitched squeaks and asthmatic rhonchi. Cases are benefited by epinephrin, aminophyllin, benadryl, and oxygen, and usually aggravated by steam.

6. *Foreign bodies* such as beads, buttons, beans, and chicken bones, if caught in the larynx, may produce all the mechanical evidences of laryngeal diphtheria. Fever may ensue and also local inflammation and infection. A foreign

edema or due to such external irritants as hot steam, may

cause enough laryngeal obstruction to require surgical intervention

8 *The laryngismus stridulus* of rickets associated with tetany may at times suggest a croupy cough and even slight laryngeal obstruction and there may be marked inspiratory stridor. Other indications of tetany, such as a positive Chvostek sign, are usually present.

IV. Post-diphtheritic Paralysis

The late type of paralysis with generalized involvement must be differentiated from other types of paralysis, particularly poliomyelitis. (See page 527.)

THE MORTALITY AND PROGNOSIS OF DIPHTHERIA

Before the use of diphtheria antitoxin became general in 1894, from 30 to 50 per cent of the diphtheria patients died In fact, in Grancher's hospital in Paris from 1884 to 1888 the mortality rate for diphtheria was 64 to 80 per cent The present rate is around 4 per cent if carriers are not included in the figures, but that of laryngeal diphtheria is appreciably higher than this, especially in cases severe enough to need intubation or tracheotomy, in some hospitals the mortality of intubated or tracheotomized patients is over 50 per cent, but other hospitals are able to hold it down to as low as 10 per cent Fifty years ago the commonest cause of death from diphtheria was suffocation; now it is failure of the circulation Formerly over 80 per cent of the deaths from diphtheria occurred in the first four years of life. In recent years, however, due to the active immunization of a large proportion of the children in most communities, far fewer cases are occurring among children and a relatively higher percentage of adults is afflicted

Prognosis in a case of diphtheria is at all times very deceptive and treacherous Sudden deaths may occur even during an apparently well-established convalescence. During the

disease such signs as the appearance of petechiæ, paralysis of the diaphragm, and a pulse-rate of less than 50, are each indicative of an almost certain fatal issue, as is also the combination of sudden abdominal pain and persistent vomiting during a seeming convalescence Patients with diphtheritic myocarditis either die or eventually make a clinically complete recovery. In general, the prognosis depends on (1) The time of administration of the antitoxin—the earlier the injection the more rapid and sure the recovery, there are practically no diphtheria deaths when adequate antitoxin is given on the first day of the disease (2) The dosage of antitoxin given and the route used for its administration (3) The virulence of the organism and the amount of toxin produced (4) The age and resistance of the patient. (5) The location of the diphtheritic lesion—the greater the extent of surface involved, the more grave the prognosis. (6) The presence or absence of secondary infection (7) The doctor There are few diseases where the doctor's skill and judgment are of such importance.

Mistakes commonly made by doctors in the treatment of diphtheria include the following (1) *Delay in suspecting the diagnosis* (2) *Delay in the administration of antitoxin* (3) *Insufficient antitoxin given in the first dose.* (4) *Wrong route used for the antitoxin* (5) *Distribution of the administration of antitoxin over several days* (6) *Improper surgical treatment, as in the use of intubation and tracheotomy* (7) *Improper after-care, as allowing exertion too soon*

THE PERIOD OF INFECTIVITY OF DIPHTHERIA

Patients are able to transmit the disease to others from some time during the twenty-four hours before the onset of symptoms until the time when the diphtheria bacilli have disappeared from the secretions of the nose and throat, or from the site of the disease if elsewhere In the majority of cases this period is less than two weeks.

ISOLATION AND QUARANTINE FOR DIPHTHERIA

Regulations vary from community to community. The following are based on those of New York City. A rigid isolation should be maintained for diphtheria patients. Beginning the fourth or fifth day of the disease, if there are no discharges (as from a running ear), nose and throat cultures are examined daily until two successive cultures, taken no less than twenty-four hours apart, are negative, at which time the patient may be released from isolation This period may not end before the seventh day of the disease and usually lasts several days more In any case most diphtheria patients should be in bed at least two weeks and the cultures are usually negative by the time they are ready to leave their beds

Pupils in the patient's family, whether they have had this disease or not, if they remain at home, may not return to school during the existence of the case At the conclusion of the case pupils may return on presentation of a certificate from the Department of Health, issued after their nose and throat cultures have proved negative

Pupils of the same family, whether they have had this disease or not, provided they are at once withdrawn from the home where the disease exists, may return to school, under these conditions: if immunized with antitoxin or if Schick-negative, after cultures from the nose and throat have proved negative, if not immunized, or if Schick-positive, on the fifth day from the last exposure, provided cultures from the nose and throat have proved negative

Children exposed at school or elsewhere than at home, whether they have had this disease or not, if they are Schick-negative or immunized, may return to school after cultures from the nose and throat have proved negative; if not immunized, or if they are Schick-positive, on the fifth day, if cultures from the nose and throat have proved negative

In instances where more than one case appears in a classroom, all the pupils in the room and the teacher should be

cultured. But when a single child in a class has developed diphtheria, and the exposure of the class was not marked, the school health officer is often justified in not culturing all the classmates, 10 per cent of whom might well be carriers but of avirulent diphtheria bacilli. However, the Schick tests should be reviewed and active immunization urged where indicated.

IMMUNITY TO DIPHTHERIA

Immunity to diphtheria can be determined by the Schick test and is of two varieties: passive and active

Passive Immunity.—This is of two types If the mother is immune, a baby before birth receives a congenital passive immunity, which is fairly complete for the first six months after birth, but in the vast majority of cases wears off during the second half of the first year. The lowest level of immunity is during the last quarter of the first year. But if the mother is Schick-positive, her new-born baby is susceptible A twenty-six-day-old infant whose mother proved to have a positive Schick test, and father a negative test but positive cultures for virulent diphtheria bacilli, developed extensive faucial and laryngeal diphtheria and died on the thirtieth day of life (W P H, 1939, No. 1915)

The second type of passive immunity may be obtained by the subcutaneous injection of 1000 to 1500 units of diphtheria antitoxin, the protection lasting from ten to twenty days. (See page 136)

Active Immunity.—This may be acquired (1) by a previous attack of the disease, though only about 50 per cent of diphtheria patients are found to be immune a year after the disease; and (2) by inoculations, using modified diphtheria toxin. There seem to be some individuals who are more difficult to stimulate to produce their own antitoxin than others, whether the stimulation be by an attack of the disease or by inoculations. *Hence, when diphtheria was prevalent,* second attacks and attacks after inoculations were not uncommon.

On the other hand, at every age there exists a percentage of individuals who are immune to diphtheria without having had either clinical manifestations of the disease or preventive inoculations. In congested districts this percentage may never be less than 50 per cent at ten years of age, increasing in adults to 70 or 80 per cent, while on the other hand, in rural communities, and in the better homes in cities, the incidence of this seemingly natural immunity remains low through childhood and even into adult life For example, before the days of general immunizations, large preparatory schools showed only 15 to 30 per cent of immune youths. The comparative immunity of those living in congested districts has been attributed to frequent exposure to the infection in doses too small to cause the disease, but enough to stimulate the production of an active acquired immunity. The widespread inoculation of infants during the past two decades and on the other hand the subsequent great reduction in the incidence of the disease and in the frequency of chance exposure have produced the result that today most children are immune and many adults are susceptible Hence, diphtheria is becoming more common in older people.

PROPHYLAXIS IN DIPHTHERIA

The Schick Test—Immunity or susceptibility to diphtheria may be determined by the Schick test. This test was first described by Schick in 1913, and consists at present of the intracutaneous injection in the forearm of 0 1 ml of a salt solution containing $\frac{1}{50}$ of a minimal lethal dose (M.L D) of diphtheria toxin A control injection distal to the test injection is done at the same time, using Schick test material in which the toxin has been inactivated by heating The injections are most readily done with a tuberculin syringe and a 27-gauge needle A positive Schick reaction is denoted by an area of redness at least 5 mm in diameter. The inflammatory reaction is present in 24 hours, and reaches its peak

on the 4th to 7th day. It then subsides, leaving a brown, pigmented spot which may persist from one to ten weeks. No reaction occurs at the control site. A positive test indicates that less than $\frac{1}{30}$ unit (probably less than $\frac{1}{100}$ unit) of antitoxin is present per ml of blood. For practical purposes such individuals may be regarded as susceptible to diphtheria, while negative reactors may be considered to be immune[1]

Pseudo-reactions are, however, sometimes seen in immune individuals, particularly adults, but rarely in small children. Pseudo-reactions are characterized by their early appearance (within eighteen hours), by an earlier peak (which is reached within thirty-six hours) and by an earlier disappearance than the true Schick reaction Any reaction persisting five days or more is a positive Schick reaction and not a pseudo-reaction A pseudo-reaction develops at the control site as well as at the site of the injection of the Schick toxin Pseudo-reactions are attributed to hypersensitivity to some product of the diphtheria bacillus The allergic state is due to previous contact with the diphtheria organism and it is very probable that pseudo-reactors possess antibacterial immunity as well as antitoxin A combined reaction is seen in subjects who are allergic to the products of the diphtheria bacillus but who do not possess circulating antitoxin A combined reaction consists of a typical pseudo-reaction at the control site and a typical Schick reaction at the test site.[2]

In hospitals for contagious diseases all non-diphtheria cases are Schick-tested on admission so that if found susceptible they can be immunized with antitoxin against a possible cross-infection with diphtheria. In private practice the

[1] The amount of antitoxin per cubic centimeter necessary to give a nega- [illegible] (0.001, 0.01

[2] The blister-like reaction which sometimes occurs when a Schick test is done in the presence of an exanthem or other generalized infection, is probably due to local tissue hypersensitivity rather than to specific susceptibility to the diphtheria toxin.

Schick test is used principally to determine whether or not immunization by the administration of toxoid or by an attack of the disease, has been accomplished, also to determine which contacts with a case are susceptible and therefore in need of protection. It is usually taken for granted, without doing an actual test, that all pre-school children, who have received no inoculations, are Schick-positive and in need of immunization

Moloney Test.—This test is carried out by intradermal injection of 0 1 cc of a 1:100 dilution of fluid diphtheria *toxoid*. A positive reaction which consists of an area of erythema developing within twenty-four hours denotes sensitization to products of the diphtheria bacillus, it probably indicates immunity on a non-antitoxic basis The test is rarely positive in very young children, a higher incidence of positivity is encountered with increasing age and a positive reaction is frequently seen among adults All persons showing a pseudo-reaction or combined reaction to the Schick test react positively to the Moloney test Occasionally an individual fails to give a positive reaction with the Schick control material but does have a positive Moloney reaction. This apparent discrepancy is due to the fact that the 1:100 dilution of toxoid used in the Moloney test contains approximately 100 times the quantity of bacterial products as does the Schick control material

Positive Moloney reactions may be regarded, for practical purposes, as indicating immunity to diphtheria It should be noted also that such individuals often react with severe constitutional symptoms following injection of the quantity of toxoid usually employed for immunization Because the percentage of toxoid-sensitive persons reaches a significant level during adolescence, the Moloney test should be employed before administering toxoid to children ten years of age or older

Active Immunization.—Diphtheria toxin is able to stimulate an individual or animal to produce his own antitoxin and therewith a usually effective immunity. The toxin is also

irritant to tissue. When toxin is treated by mixing with antitoxin in given proportions to form toxin-antitoxin, or is attenuated to form toxoid by aging, by heating to 54° C. or by combining with chemicals such as formaldehyde, the irritant and toxic effects may be markedly neutralized while the stimulating effect will still persist. Thus various preparations are available for active immunization against diphtheria

Toxin-antitoxin —A mixture of toxin and antitoxin, called toxin-antitoxin, was the original preparation used for the immunization of non-immune people (first in 1913 by Von Behring), but its use has been replaced by that of a toxoid Toxin-antitoxin mixtures had two disadvantages in comparison to the present toxoids; they contained a heterogenous serum, usually equine, which occasionally sensitized patients to that serum, and they produced a lower percentage of immune reactions in children

Toxoid —Toxoid is usually prepared from strong toxins to which is added 0 4 per cent of formaldehyde, the mixture being kept in an incubator at 39° C. for one month or more until the product is thoroughly detoxified The advantages of toxoid over toxin-antitoxin are that its preparations are more stable, the immunity produced is more certain and more rapid, immunizing sometimes in a month or two, and in particular serum sensitization is avoided However, in older children and adults local and systemic reactions are somewhat common Such individuals should first have a Moloney test done After a positive Moloney test the first injection of the undiluted toxoid should not be larger than 0 05 ml. Otherwise, the dosage recommended for primary immunization is three intramuscular injections of 0 5 ml each at intervals of a month

Toxoid, Alum Precipitated —This is made by adding 1.5 per cent solution of alum to fluid toxoid, causing a precipitation of the toxoid The precipitate is the active immunizing agent and because of its slow absorption has greater immunizing power than a clear solution of toxoid.

TABLE 5.—PREPARATION AND STANDARDIZATION OF BIOLOGICAL PRODUCTS EMPLOYED IN PROPHYLAXIS AND TREATMENT OF DIPHTHERIA

	Preparation	*Standardization*
Toxin	Organism in broth incubated 34° C for 7 days Filtered to remove bacilli	1 By determining the minimal lethal dose (M L D) This is the least quantity of toxin which will kill a 250-gm guinea pig in 96 hours 2 By determining the Limes plus dose (L +) This is the least quantity of toxin which kills a 250-gm guinea pig after the addition of 1 unit of standard antitoxin supplied by the National Institute of Health
Schick test	Toxin plus 0 25% peptone and salt solution	Each 0 1 ml contains 1 50 M L D of toxin The test is performed by injecting 0 1 ml of the solution *intradermally* in the person to be tested
Schick test control	Schick test solution heated to 75° C for 5 minutes	The test is performed by injecting 0 1 ml of the solution *intradermally* in the person to be tested
Antitoxin	Horses are injected subcutaneously with from 1 to 10 M L D of toxin Increasing doses of toxin are given every day until antitoxic content of horse's blood reaches at least 500 units per cc Horse serum is refined	By determining neutralizing action when combined with toxin which has been standardized against standard antitoxin The antitoxic unit is calculated from the smallest amount of test antitoxin *protecting* a 250-gm pig for 4 days against the L + dose of standard toxin
Toxin-antitoxin	Toxin plus antitoxin to give 0 1 L + dose of toxin per cu cm	5-ml doses of the mixture produce diphtheria poisoning and death in guinea pigs in 4 to 5 days
Toxoid	Toxin plus 0 4% formaldehyde Incubated at 39° C for 6 weeks	One dose of 1 ml shall protect 80% of a group of guinea pigs against 5 M L D of toxin after 6 weeks
Alum-precipitated toxoid	Toxoid plus aluminum potassium sulphate Remove supernatant Wash and dilute precipitate and salt solution	One dose of 1 or ½ ml shall produce 2 units of antitoxin in the blood of a guinea pig after 4 weeks
Moloney test	1 100 dilution of fluid toxoid	0 1 ml intradermally, read 24 hours later Positive test consists of erythema greater than 10 mm

irritant to tissue When toxin is treated by mixing with antitoxin in given proportions to form toxin-antitoxin, or is attenuated to form toxoid by aging, by heating to 54° C. or by combining with chemicals such as formaldehyde, the irritant and toxic effects may be markedly neutralized while the stimulating effect will still persist. Thus various preparations are available for active immunization against diphtheria

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Toxoid.—Toxoid is usually prepared from strong toxins to which is added 0 4 per cent of formaldehyde, the mixture being kept in an incubator at 39° C for one month or more until the product is thoroughly detoxified The advantages of toxoid over toxin-antitoxin are that its preparations are more stable, the immunity produced is more certain and more rapid, immunizing sometimes in a month or two, and in particular serum sensitization is avoided However, in older children and adults local and systemic reactions are somewhat common Such individuals should first have a Moloney test done After a positive Moloney test the first injection of the undiluted toxoid should not be larger than 0 05 ml Otherwise, the dosage recommended for primary immunization is three intramuscular injections of 0 5 ml each at intervals of a month

Toxoid, Alum Precipitated —This is made by adding 1 5 per cent solution of alum to fluid toxoid, causing a precipitation of the toxoid. The precipitate is the active immunizing agent and because of its slow absorption has greater immunizing power than a clear solution of toxoid.

ceptible at eighteen months. It is now generally recommended that active immunization against diphtheria be started at three months of age It is nearly universal practice to immunize against diphtheria, tetanus, and pertussis simultaneously. We have found the following schedule to be satisfactory: At three months of age 0 5 ml. of alum precipitated or aluminum hydroxide-adsorbed diphtheria and tetanus toxoids containing also at least 4 antigenic or protective units of pertussis vaccine is injected intramuscularly into the left gluteus maximus At four months of age the dose is repeated, using the right gluteus maximus as the site of injection At five months of age the dose is repeated, the inoculation being made in the left vastus lateralis muscle, or in the left gluteus maximus At eighteen months of age a recall (booster) injection is given into the right gluteus maximus or the right deltoid employing the same material and the same dosage as previously Some physicians use fluid toxoid for this and for all subsequent recall injections At 3½ years of age 0 5 ml of the combined antigens is given into the left deltoid With this same dosage a third recall injection is given when the child is six years old, and a fourth when he is nine

At twelve years of age the child is given a Schick test as well as a Moloney test for sensitivity to toxoid. If the Schick test is negative, no further immunization need be attempted If the Moloney test is positive, indicating sensitivity to toxoid and latent immunity, no further injection is required, regardless of the result of the Schick test The toxin of the Schick test usually provides an adequate recall dose for persons who are toxoid-sensitive If the child is Schick positive and Moloney negative, a recall injection of 0 3 ml of alum precipitated diphtheria toxoid is given (combined diphtheria and tetanus toxoid may be used, but pertussis vaccine is not included) At sixteen years of age the patient is again tested, and the same indications for giving or withholding toxoid are followed.

Three intramuscular doses of 0.5 ml. each of alum precipitated toxoid at intervals of one month comprise the method of primary active immunization now preferred by many public health authorities. This preparation being a precipitate in suspension, a needle no finer than 23 gauge should be used Reactions in infants are apparently comparable to those from plain toxoid, but in addition there may be a hard lump at the site of the injection due to the slow absorption of the alum-toxoid combination. In rare instances this may break down to form a sterile abscess. In adults, the alum preparation is especially liable to cause unpleasant reactions, hence they should receive the plain liquid toxoid It is probably wise to give the toxoid into the deltoid muscle in older children and adults, but in infants and very young children it is preferable to inject the toxoid, either plain or alum precipitated, deep into a buttock muscle. Reactions are minimal; definite abscesses are rare although firm lumps result, and the infant is much less frightened and easier to control

Toxoid, Aluminum Hydroxide-adsorbed.—This preparation contains the toxoid adsorbed onto aluminum hydroxide Like alum precipitated toxoid, it is more slowly absorbed into the blood after injection than is fluid toxoid, and its effectiveness as an immunizing agent is thereby enhanced. Some physicians prefer aluminum hydroxide-adsorbed to the alum precipitated variety because they believe that fewer local reactions occur with the aluminum hydroxide-adsorbed preparation, and because the actual injection of this preparation is less painful

Program of Active Immunization —Infants are immune to diphtheria at birth if their mothers are immune. This is a passive form of immunity dependent upon antitoxin transferred from the mother's blood across the placenta The antitoxin titer of the newborn baby's blood is usually the same as that of the mother, but it declines at such a rate that at six months of age 50 per cent of infants are susceptible as judged by the Schick test, and about 70 per cent are sus-

ceptible at eighteen months. It is now generally recommended that active immunization against diphtheria be started at three months of age. It is nearly universal practice to immunize against diphtheria, tetanus, and pertussis simultaneously. We have found the following schedule to be satisfactory: At three months of age 0.5 ml. of alum precipitated or aluminum hydroxide-adsorbed diphtheria and tetanus toxoids containing also at least 4 antigenic or protective units of pertussis vaccine is injected intramuscularly into the left gluteus maximus. At four months of age the dose is repeated, using the right gluteus maximus as the site of injection. At five months of age the dose is repeated, the inoculation being made in the left vastus lateralis muscle, or in the left gluteus maximus. At eighteen months of age a recall (booster) injection is given into the right gluteus maximus or the right deltoid employing the same material and the same dosage as previously. Some physicians use fluid toxoid for this and for all subsequent recall injections. At 3½ years of age 0.5 ml. of the combined antigens is given into the left deltoid. With this same dosage a third recall injection is given when the child is six years old, and a fourth when he is nine.

At twelve years of age the child is given a Schick test as well as a Moloney test for sensitivity to toxoid. If the Schick test is negative, no further immunization need be attempted. If the Moloney test is positive, indicating sensitivity to toxoid and latent immunity, no further injection is required, regardless of the result of the Schick test. The toxin of the Schick test usually provides an adequate recall dose for persons who are toxoid-sensitive. If the child is Schick positive and Moloney negative, a recall injection of 0.3 ml. of alum precipitated diphtheria toxoid is given (combined diphtheria and tetanus toxoid may be used, but pertussis vaccine is not included). At sixteen years of age the patient is again tested, and the same indications for giving or withholding toxoid are followed.

It should be noted that the development of an antitoxin titer sufficient to give a negative Schick test after immunization *with toxoid* does not guarantee permanent *immunity* against diphtheria. An appreciable number of infants revert to Schick-positivity within a year, and by the end of three years, the number of those who are again Schick positive is of definite practical signficance; hence the importance of recall (booster) injections of toxoid at intervals of three years or less The effectiveness of diphtheria toxoid is indicated by the fact that it has been shown to be more effective in producing antibodies than is an attack of clinical diphtheria

Primary immunization of children not immunized in infancy should be carried out in the same manner as that described in the program outlined above with the following exceptions:

1 The deltoid and triceps muscles should be injected, rather than the gluteus maximus or vastus externus

2 Diphtheria toxoid should not be given to children ten years of age or older without a Schick test and a Moloney test

3 (*a*) If the child is Schick positive and Moloney negative, immunize by 3 injections of 0 5 ml. of diphtheria toxoid (or diphtheria combined with tetanus toxoid) at intervals of one month

(*b*) If he is Schick negative, give no toxoid regardless of the result of the Moloney test

(*c*) If he is Schick positive and the Moloney test is strongly positive, give no further injections, since the Schick and Moloney tests furnish sufficient stimulus for adequate antitoxin production, and antibacterial immunity is probably present also

(*d*) If the child is Schick positive and the Moloney test is only moderately positive, immunize with highly purified fluid diphtheria toxoid Give 0 05 ml subcutaneously as first dose. Double the dose at weekly intervals, provided marked reaction does not occur, until

4 injections totaling 0.75 ml have been given The Schick test should be repeated in three months

Since active immunization against diphtheria first was described, which was in 1914 (Park and Zingher), the incidence of diphtheria has been markedly reduced and in many cities where there have been well-managed campaigns for the immunization of all children, diphtheria has been practically wiped out The number of cities in the United States that have had no cases of diphtheria for the least twelve months grows steadily from year to year

In New York City the Department of Health's educational campaign for immunization against diphtheria began in 1929 The effectiveness of this campaign is indicated by the fact that between 1920 and 1929 there were on the average 10,685 cases of diphtheria each year with an annual average of 684 deaths For the period of 1935 to 1939 these figures had fallen to an average of 952 cases and 42 deaths per year Between 1950 and 1954 the number of cases of diphtheria in New York City per year varied from 18 to 72 and there have been no more than 2 deaths from diphtheria in any year since 1950. In 1955, there were 22 cases and for the first time in the history of Greater New York, no deaths from this disease

Prevention of Spread of Diphtheria —The diphtheria patient should be quarantined until three successive cultures of the nose or throat or other infected area, taken at intervals of twenty-four hours, are negative In 80 per cent of cases cultures are negative within three weeks of onset of diphtheria Of the remaining 20 per cent, most become free of diphtheria in the subsequent two or three weeks, but a few remain carriers of virulent diphtheria bacilli for many weeks and even months Such carriers should receive procaine penicillin, 300,000 to 600,000 units daily for seven days, which is generally effective If this treatment fails, aureomycin (or other tetracycline drugs) in a dosage of 25 mgm per kilo of body weight per day may be given for one week If this treatment fails, tonsillectomy and adenoidectomy

should be considered. This procedure followed by irradiation of the nasopharynx by radon has been successful in a number of cases under our care

All family and other persons in close contact with diphtheria patients should be cultured for the presence of virulent C. diphtheriæ All contacts who are school children and adults who are food handlers should be quarantined until two successive daily throat and nose cultures are negative.

Up to 10 per cent of diphtheria patients are secondary cases in families in which there has been a primary case within the preceding thirty days In order to minimize this spread of diphtheria every effort should be made to protect those in close contact with diphtheria patients Children who have previously received adequate active immunization should be given a recall injection of 1 0 cc. of fluid diphtheria toxoid subcutaneously. An antitoxin titer rise to effective levels will occur within forty-eight hours, thereby affording protection, since the incubation of diphtheria varies between two and five days. Children who have not been immunized should be given 2,000 units of antitoxin intramuscularly after being tested for sensitivity to horse serum, and active immunization with toxoid should be started at the same time Since many adults are known to be susceptible to diphtheria at the present time, they too should receive diphtheria antitoxin if they have been in close contact with a diphtheria patient It should be remembered that the passive immunity afforded by diphtheria antitoxin does not last beyond two weeks If exposure continues beyond this time the dose should be repeated Diphtheria has occurred as early as the seventh day after a prophylactic dose of antitoxin (W P H , 1933, No 3160), but it is unusual in less than three weeks

In one city it has been found that of the children ten years of age or under who were exposed to diphtheria in their own families, 10 per cent of those not given prophylactic antitoxin developed diphtheria, whereas only 1 2 per cent of those who received this prophylactic treatment were attacked.

THE TREATMENT OF DIPHTHERIA

Specific Treatment

Diphtheria antitoxin should be administered as soon as possible, following skin or conjunctival test for sensitivity to horse serum. If the presence of diphtheria is suspected, antitoxin should be given at once, and the diagnosis established later.

Diphtheria antitoxin has principally a neutralizing effect checking further damage to the organism by the toxin. Its curative effect, strictly speaking, is limited, since it cannot affect toxin already tied up in tissue cells If no antitoxin is present to counteract the toxin as it is formed, the toxin will quickly combine with the tissues, notably the heart muscles and motor nerve fibers, hence antitoxin should be given to the diphtheria patient at the earliest possible moment. When given intravenously antitoxin is immediately available for counteracting toxin, when given intramuscularly a maximum of blood concentration is reached within twenty-four hours, when given subcutaneously a maximum concentration of antitoxin in the blood is not reached for about thirty-six hours Therefore, antitoxin should be given intravenously to critically ill patients, to those with laryngeal diphtheria, to those who have been sick several days, to those whose diphtheria is a complication of some other disease, and particularly to small children where the danger of severe serum reactions is less marked It is usually given intramuscularly to average cases seen early and for such an injection the vastus lateralis muscles or those of the buttocks may be used. It should never be given subcutaneously for therapeutic purposes

Before the antitoxic serum is given, the precautions described in the chapter on Serum Reactions should be carefully observed, including tests for sensitization and having epinephrin immediately available When there is reason to fear a bad reaction if a horse serum is given, bovine diphtheria antitoxin is sometimes obtainable.

The dosage of antitoxin for the treatment of diphtheria should never be less than 10,000 units, and it is rarely necessary to give more than 80,000 units, particularly if at least one-half of this is given intravenously Thus, the minimum dose for a comparatively early case of faucial diphtheria is 10,000 units intramuscularly The total amount of antitoxin needed should be given at the first injection, and for intravenous injection it is well to dilute the serum with 5 per cent glucose solution or with physiological saline solution and to administer it by slow drip A child should receive as much as an adult because, although the body is smaller, the quantity of diphtheria toxin produced is the same and the disease in a child is relatively more severe Indications that enough antitoxin has been given can usually be detected eighteen to twenty-four hours after its administration They include the findings that the diphtheritic membrane has not spread but is growing smaller, and that the patient feels generally better and has less fever If these indications are not present, more antitoxin should be given, but a second dose of antitoxin is an indication that not enough was given in the first dose

The following schedule of antitoxin dosage may be used

Location of Lesion	*Dosage*	*Route*
Tonsils only	10–20,000 units	Intramuscularly
Anterior nasal	10–20,000 units	Intramuscularly
Pharynx or uvula	20–40,000 units	Intramuscularly
Larynx	20–40,000 units	Intravenously
Nasopharynx	40–80,000 units	Intravenously, or half intramuscularly and half intravenously
"Bull-neck" diphtheria	80–100,000 units	Intravenously, or half intramuscularly and half intravenously

Some patients who recover from diphtheria with antitoxin treatment are found to be Schick positive. For this reason some physicians give toxoid as well as antitoxin to all patients with diphtheria The first dose of toxoid is given one week after antitoxin has been administered and the second and third doses one and two months later

Although various strains of diphtheria bacilli vary markedly in their virulence, and although cases of unusual virulence have recently been reported particularly in Europe, the present standard antitoxins are suitable for treatment of the disease due to any strain (Povitzky *et al.*)

Penicillin possesses some activity against the diphtheria bacillus, but it is not effective enough to be used without antitoxin in the treatment of diphtheria Penicillin is useful, however, in two ways it decreases the percentage of patients who remain carriers after recovery and it is effective against the beta-hemolytic streptococci which are frequently secondary invaders Procaine penicillin, 300,000 to 600,000 units daily should be given by intramuscular injection The tetracycline group of antibiotics may be used instead of penicillin in dosage of 40 to 50 mgm per kilogram of body weight daily. The sulfonamides are ineffective against C diphtheriæ and its toxin

General Treatment

The doctor caring for a diphtheria patient should keep careful watch of the diphtheritic membrane and its extent and condition, of the ear drums, of the cervical lymph nodes, of the lungs; of the heart, noting particularly the size, rate, rhythm, and the quality of the sounds, of the muscle power, particularly of the soft palate and the eyes, of the urinalysis, and finally of the bowels.

The diphtheria patient should be kept flat in bed for at least twelve days Quiet is very important, but gentle entertainment is better than fretful restlessness In cases where antitoxin was given late, for instance on the fourth or fifth day of the disease, or where the heart sounds have been in any way abnormal in rhythm, rate, or quality, the stay in bed should be prolonged until all evidence of myocardial involvement is past Electrocardiographic examinations should be made at frequent intervals in order to exclude abnormalities which may not be detectable by physical exam-

The dosage of antitoxin for the treatment of diphtheria should never be less than 10,000 units, and it is rarely necessary to give more than 80,000 units, particularly if at least one-half of this is given intravenously Thus, the minimum dose for a comparatively early case of faucial diphtheria is 10,000 units intramuscularly. The total amount of antitoxin needed should be given at the first injection, and for intravenous injection it is well to dilute the serum with 5 per cent glucose solution or with physiological saline solution and to administer it by slow drip. A child should receive as much as an adult because, although the body is smaller, the quantity of diphtheria toxin produced is the same and the disease in a child is relatively more severe. Indications that enough antitoxin has been given can usually be detected eighteen to twenty-four hours after its administration. They include the findings that the diphtheritic membrane has not spread but is growing smaller, and that the patient feels generally better and has less fever If these indications are not present, more antitoxin should be given, but a second dose of antitoxin is an indication that not enough was given in the first dose.

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Some physicians believe that intravenous administration of dextrose tends to counteract the damage done to heart muscle by diphtheria toxin. The evidence for this belief is not well founded, and the possible benefit must be balanced against the disadvantage of frightening and exciting the patient.

Difference of opinion also exists regarding the use of digitalis in diphtheritic myocarditis, some authors contending that this drug is contraindicated in diphtheria because it might be synergistic with diphtheria toxin in delaying cardiac conduction. We believe that digitalis has a definite place in the treatment of diphtheritic myocarditis We give digitalis to all patients showing electrocardiographic or clinical signs of moderately severe or severe myocarditis, even when no evidence of cardiac decompensation is present Thus, digitalization is begun if the electrocardiogram shows definitely abnormal QRS complexes, or prolonged P–R intervals, or ectopic foci, or complete heart block Similarly, digitalis is used if the first heart sound at the apex is greatly diminished or if sounds caused by premature contractions are heard, or if clinical evidence of cardiac decompensation is obtained The value of digitalis used in this manner is difficult to demonstrate by statistical analysis, but careful observation of over 300 diphtheria patients treated with digitalis has left us with the strong clinical impression that it is of value in diphtheritic myocarditis

Many forms of digitalis may be employed, but we believe that digoxin is the most satisfactory preparation. The dosage of digoxin needed for digitalization varies considerably from patient to patient, children of the same body weight may require quite different quantities of the drug In general, infants need a relatively larger dose than do older children and adults The exact dosage of digoxin must therefore be determined for each child. However, we have found that the following dosage schedule may be used as a rough guide·

Infants under the age of two years are given a total digitalizing dose of 75 micrograms (075 mgm) per kilogram

ination. Several instances have been observed where patients have left their beds too soon and have suffered sudden death from myocardial failure.

The diet should consist of fluids and soft solids throughout the period of fever and as long as swallowing is difficult The patient should not be allowed to feed himself until damage to the heart has been ruled out Extra fluids are desirable unless there is some heart involvement Very hot and very cold drinks are more gratefully received than those of intermediate temperature

Irrigations of the throat, using a salt and soda solution, 1 teaspoonful of each to 1 quart of water as hot as the patient can tolerate, are very helpful in relieving the pain. Some small patients prefer a weak glucose solution The patient should certainly not be allowed to sit up for these irrigations but should lie either on his side in bed or face down with his head beyond the side of the bed Painting with antiseptics or swabbing areas of diphtheritic infection is not advisable because of the dangers of causing trauma and opening up new channels of infection For the same reason suspected peritonsillar abscesses should certainly not be incised in the presence of a diphtheritic infection An ice collar brings comfort when there is pain from swollen cervical lymph nodes. It is also beneficial in combating the inflammation

For malaise codeine is occasionally necessary but aspirin is usually sufficient Morphine and other strong sedatives are contraindicated as they may mask symptoms, especially those of laryngeal obstruction Where superimposed infection is suspected, penicillin or other antibiotics may be very beneficial

Treatment of Diphtheritic Myocarditis.—The same principles of therapy are used in diphtheritic myocarditis as those in other etiologic types of myocarditis A regimen of absolute rest is essential as long as evidence of myocarditis is present. The patient should move about in bed as little as possible, and he should not feed himself. He must not be permitted to sit up to use a bed pan, or for any other purpose.

latory collapse which may occur in meningococcemia, (see page 420).

Treatment of Diphtheritic Paralysis—There is no specific treatment, no drugs having any effect upon the involved nerves. Paralysis or weakness of the extremities requires rest, perhaps temporary splinting, and proper physical therapy. Weakness of the palate, or of the pharyngeal muscles severe enough to interfere seriously with swallowing and to cause danger of aspiration requires treatment by nasal gavage For this purpose a polyethylene tube is best, since it may be allowed to remain in place for three or four days at a time without causing injury If the muscles of respiration are involved, a tank respirator or other form of respiratory aid may be necessary. As long as difficulty in swallowing or breathing is present, antibiotics should be given in prophylactic dosage, in order to decrease the danger of the occurrence of pneumonia. The diet should be of high caloric content, and rich in protein, and vitamins and iron salts should be supplied. The patient may be encouraged by the assurance that complete recovery occurs in the vast majority of cases

Special Treatment of Laryngotracheobronchial Diphtheria—Patients with this form of diphtheria must be regarded as seriously ill, they require the most expert medical and nursing care. They should receive diphtheria antitoxin (40,000 units intravenously) as soon as possible, but it should be realized that this will not diminish the obstruction to the airway for at least eighteen hours Antitoxin will not affect toxin which has become fixed in cells, hence the antitoxin cannot undo the injury already done to the mucosa of the larynx and trachea, it can only prevent further damage It is wise therefore, to expect some degree of decrease in the patency of the airway for eighteen to twenty-four hours after antitoxin has been given

Every effort should be made to calm the patient with laryngeal obstruction, and to decrease his fear as much as possible Crying, and apprehension increase the respiratory

of body weight by intramuscular injection This total quantity is given in three divided doses at six-hour intervals Twenty-five to thirty per cent of the digitalizing dose is given each day by injection or by mouth as a maintenance dose For children three to five years of age, the digitalizing dose required is in the neighborhood of 60 micrograms (.06 mgm) per kilogram of body weight, given in three intramuscular injections at six-hour intervals. Twenty-five per cent of the digitalizing dose is given daily for maintenance of digitalization. For children over five years of age, the digitalizing dose is roughly 50 micrograms (.05 mgm.) per kilogram of body weight, administered in the same manner as described above, and 25 per cent of the digitalizing dose is given as a maintenance dose daily

All adults are given the same dose of digoxin regardless of their weight. Two methods of administration are employed In the first, 1 5 mgm. of digoxin are given by mouth as an initial dose, followed by .25 mgm every six hours until the desired ventricular rate is reached In the second method, an initial dose of 0 5 to 1 0 mgm is given intravenously, and if required, additional doses of 0 25 mgm are given every six hours by mouth The maintenance dose of digoxin for adults is from 0 25 to 0.5 mgm daily

Nausea, vomiting and cardiac arrhythmias are signs of toxicity due to digoxin, but ST segment and T-wave changes are indicative of digitalis effectiveness and are not necessarily evidence of over-dosage

When myocardial decompensation does occur in diphtheria, it should be treated the same as is cardiac insufficiency due to other causes, digitalis, oxygen therapy, morphine, a salt-poor diet, and diuretics being employed.

When shock and peripheral circulatory collapse complicate diphtheria, attempts should be made at once to raise the blood pressure and restore blood volume. Plasma and blood should be given intravenously, and nor-epinephrine, epinephrine, or ephedrine should be administered. Cortisone should be given in the same manner as in the treatment of the circu-

sufficient patency of the airway. However, this method has two serious defects: it may fail if the membrane is very firmly attached to the underlying mucosa, and manipulation and aspiration of the membrane may be followed by so much edema that the obstruction is not decreased

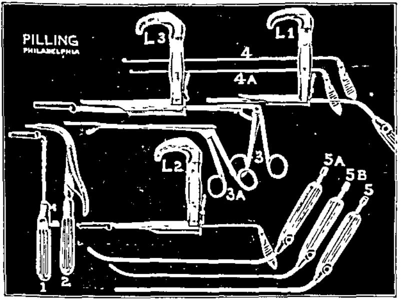


FIG 14 —Instruments used in the suction and intubation treatment of croup L 1, L2, and L3 Jackson laryngoscopes 1, O'Dwyer intubator with small-sized tube, 2, O'Dwyer extubator, 3, and 3A, direct or visual intubators for use with the laryngoscope, 4, and 4A, direct or visual hook extubators, 5, 5A, and 5B metal suction tubes, A and B with flexible tips for bronchial suction Instruments made by the G P Pilling & Son Co Philadelphia

Intubation —Intubation of the larynx is the second method for relief of obstruction to be considered It consists of the insertion of a hollow tube, such as that perfected by O'Dwyer (see "Tube Room Technique," page 574) The tube extends just above, and just below the larynx, thus providing an

exchange required. In the presence of a narrowed airway this increase is accomplished only by greatly increased work of respiration, thus setting up a very unfavorable cycle A plastic tent into which steam is introduced or fine droplets of cold water are blown by a vaporizer or nebulizer is essential The moistened atmosphere decreases the viscosity of the secretions in the larynx and trachea, so that they are *more readily removed by coughing.*

Signs of increasing respiratory distress must be sought constantly An experienced observer is required to determine whether the airway has become so narrow that intervention to relieve the obstruction is needed In general, if the patient remains quiet, and calm, and is able to rest and sleep it is almost certain that no intervention is yet necessary. *On the other hand, increasing restlessness and anxiety, and* inability to sleep except in short snatches usually indicate that respiratory needs are not being met. Increasing retraction of the lower end of the sternum and of the suprasternal notch are also indicative of increasing obstruction It should be noted that the patient with an airway too narrow to supply his needs is suffering from carbon dioxide accumulation as well as hypoxia. Another important concept to be borne in mind is that cyanosis is a late symptom of obstruction, and means that respiratory decompensation is present Absence of cyanosis does not necessarily mean that the child has an adequate airway, on the other hand, the presence of cyanosis means that the patency of the airway must be increased at once.

Since the degree of restlessness and distress are the best index of the patient's condition, the physician should withhold sedatives and hypnotics, which would obscure these symptoms.

Three methods may be used for relief of respiratory tract obstruction. The first is by means of *aspiration* of the diphtheritic membrane and secretions in the larynx under direct observation with the laryngoscope. *Performance of this* procedure, one or more times, may be sufficient to insure

to be replaced either at once or presently. To prevent ulceration it is well anyway to replace a tube every five or six days. It is probably the best practice not to allow intubation tubes to be worn longer than ten days altogether, or to intubate a child more than six or seven times. If there is still laryngeal obstruction at the end of this period the

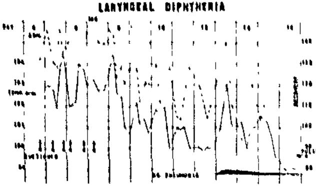


FIG. 15. Showing a case of laryngeal diphtheria in a child, aged six years, treated by antitoxin intravenously and six suctions, and complicated by a short attack of bronchopneumonia during the convalescence.

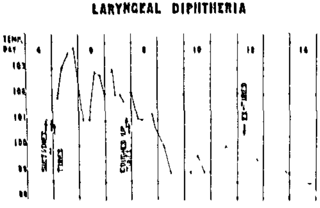


FIG. 16. Showing a case of laryngeal diphtheria in a boy, aged five years, treated successfully by antitoxin intravenously, suction and intubation.

airway through this obstruction There are many disadvantages to this method including: (1) The tube does not relieve obstruction in the trachea; (2) it cannot be used when there is marked edema of the supraglottic tissues such as the arytenoids which might close over the top of the tube; (3) while wearing the tube the child must be under the constant supervision of someone capable of removing the tube on an instant's notice, in case it should become plugged up by a piece of membrane or a mass of tenacious mucus, (4) tubes are frequently coughed up, sometimes to release membrane coming up from below, and often need to be replaced within a very few minutes, otherwise the larynx might contract and prevent the passage of any air whatever, (5) when it has been necessary to intubate a child several times, the resulting *inevitable injury to the tissues of the larynx is apt to cause* scar formation and contraction, resulting in a more or less permanent and complete obstruction unless a tube is worn constantly

Intubation may be done by the indirect or tactual method using O'Dwyer's instruments (1 and 2, Fig. 13) or by the direct or visual method with a laryngoscope (3 and 3A, Fig 13) Skill should be acquired in the anatomy laboratory before attempts are made to intubate a patient.

The management of an intubated child requires special skill. If any food enters or passes through the intubation tube the child may either cough up the tube or develop an aspiration pneumonia Accordingly, it is usually necessary to feed intubated children by means of nasal gavage A liquid diet can thus be easily given a small child Older children who have worn an intubation tube for some days are frequently able to swallow soft solids placed in their mouths, especially if they are strong enough to sit erect for their meals

After an acute case of laryngeal diphtheria, an intubation tube can usually safely be withdrawn when the temperature has returned to normal, that is, after the tube has been worn five or six days In possibly a third of the cases it may have

to be replaced either at once or presently. To prevent ulceration it is well anyway to replace a tube every five or six days. It is probably the best practice not to allow intubation tubes to be worn longer than ten days altogether, or to intubate a child more than six or seven times. If there is still laryngeal obstruction at the end of this period the

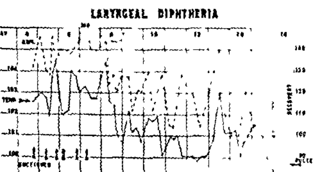


FIG. 15.—Showing a case of laryngeal diphtheria in a child aged six years treated by antitoxin intravenously and six suctions, and complicated by a short attack of bronchopneumonia during the convalescence.

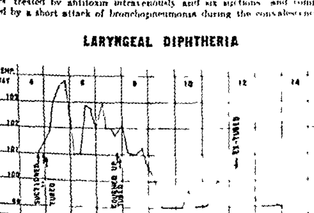


FIG. 16.—Showing a case of laryngeal diphtheria in a boy aged five years treated successfully by antitoxin intravenously, suction and intubation.

larynx should be given a complete rest and a tracheotomy should be done.

Tracheotomy, the third method for relief of obstruction is the safest and most effective, in our present opinion. This is in part due to the fact that, diphtheria having become a comparatively rare disease, intubation is now a vanishing art. In addition, tracheotomy entails none of the disadvantages of the other methods, a consideration which greatly outweighs the fact that it is a surgical operation. Tracheotomy is performed under local anesthesia. Danger of such complications as pneumothorax and pneumomediastinum is greatly lessened if the operation is performed with a minimum of dissection. Tracheotomy permits removal of membrane from the trachea and bronchi, and bits of membrane which are coughed up are easily removed by aspiration with a catheter. It is advisable for a few days after operation to keep the patient in an atmosphere moistened by steam or small droplets of water (croup tent). Prophylactic doses of antibiotics should be given while the tracheotomy tube is in place to reduce the possibility of the occurrence of bronchopneumonia. Generally, the tube can be removed within a week after its insertion.

DIPHTHERIA CARRIERS

Three weeks after the onset of a case of diphtheria about 80 per cent of the cases will give cultures negative for the presence of the diphtheria bacillus. Of the remaining 20 per cent, most will become free from the bacilli in the course of time but a few patients may drag on for weeks as carriers of the organism and therefore as potential sources of danger. Healthy people may also be found harboring diphtheria bacilli in their throats or noses and may be capable of giving the disease to others without contracting it themselves. Many of the diphtheria bacilli that are found in these so-called carriers can be shown by guinea-pig tests to be non-virulent and incapable of causing disease. Of diphtheria bacilli found

in the throats of a general population not known to have been exposed to the disease, less than 10 per cent will be found to be virulent, and accordingly carriers found in a general population might well be considered merely "presumptive carriers" until a virulence test on their bacilli has been found positive. On the other hand the great majority of the bacilli that are found in the throats of convalescent patients, and in the throats of healthy carriers who have been in contact with cases of the disease, are virulent organisms. Accordingly all the carriers of these latter two groups should be isolated until they are no longer carriers or until the bacilli have been proved to be non-virulent.

Penicillin has been found by some authors to be effective in eliminating the carrier state[1]; more recent experience, however, has thrown some doubt on the effectiveness of penicillin in freeing the nose and throat of diphtheria bacilli. Carriers should receive 300,000 to 600,000 units of aqueous procaine penicillin intramuscularly daily for several days or the antibiotic may be given by mouth in a daily dose of 600,000 to 800,000 units. If virulent diphtheria bacilli are still present in the nose and throat at the end of this time, one of the tetracycline drugs (25 mg. per kg. of body weight per day) should be given for one week. If this treatment fails, tonsillectomy and adenoidectomy should be considered. This procedure, followed by radon or roentgen-ray irradiation of the nasopharynx, has been effective on a number of occasions in our experience.

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5

Vincent's Angina

Synonyms —Ulceromembranous angina, Fusospirochetosis (pharyngeal)

Definition.—Angina (properly pronounced An′-jina) is any disease, but particularly one of the fauces, attended by a sense of strangling pain or suffocation. Vincent's angina is a specific infectious ulceromembranous disease of the tissues of the pharynx caused by symbiosis of the fusiform bacillus and the Spirochæta vincenti The disease was first identified as a clinical entity by Vincent in 1896, but in 1894 Plaut had mentioned the occurrence together of the two microörganisms in certain throat conditions, and his name is occasionally associated with that of Vincent in the *title of* the disease.

THE ETIOLOGY OF VINCENT'S ANGINA

Exciting Cause.—This infection is caused by two separate and distinct microorganisms growing together, a fusiform bacillus (Fusobacterium plauti-vincenti) and the Spirochæta or Spirillum vincenti It is probable that the bacillus is a normal inhabitant of most mouths, but that in this and certain other diseases of the mouth the spirillum breaks down tissue resistance, making infection by the bacillus possible

The two organisms are found together in a number of conditions besides Vincent's angina The infection of the gums known as "trench-mouth" is due to these two organisms, and they are also found together in various lesions of the mouth in cases of agranulocytic *angina, leukemia, and the other* blood dyscrasias.

Bacteriology.—Both organisms are anaerobic, and they can be grown under anaerobic conditions, in media containing serum. However, bacteriologic diagnosis is more easily made by examination of smears rather than of cultures.

To prepare smears, the ulcerated area is first cleaned by gargling or irrigating the throat and mouth with a hot solution of sodium bicarbonate in water. With a swab, the cheesy exudate is scraped aside and some of the underlying



Fig 17.—Showing fusiform bacilli and tangled masses of the spirilli, from a case of ulcerative stomatitis due to the infection with the Vincent's microorganisms (Todd and Sanford, Courtesy of W B Saunders Company)

material is transferred onto a clean glass slide by rolling the swab in streaks along the slide, not by rubbing the swab on the slide. The preparation is stained with any simple stain, such as methylene blue. The customary appearance is of many pus cells, mucus, and cellular detritus with scattered bacteria of various sorts, but with the two specific microorganisms usually present in considerable number, particularly just beyond the margins of masses of material

on the slide. The fusiform bacillus is Gram-negative, spindle-shaped, and rather long, tapering at each end and rather thick in the center. The length varies from that of the diameter of a leukocyte (10 to 15 microns) to one-half as much The spirillum or spirochete of Vincent is a somewhat irregular spiral form, one to two times as long (10 to 25 microns) as the fusiform bacillus, and with 8 to 15 curves It is also Gram-negative, but does not stain as well as the bacillus In smears these spirillæ are sometimes rather hard to find, having a moderate resemblance to the lines in the preparation caused by the presence of mucus.

Predisposing Factors —Vincent's angina is spread by close contact, particularly by kissing, by eating-utensils, and by droplet infection Factors that reduce the resistance of the mouth, such as decayed teeth, irregular or diseased tonsils, and chronic illness all predispose to the disease. All ages are susceptible, but the incidence is especially high in men, and in children in institutions, probably due to deficient care in the cleanliness of the mouth

IMMUNITY TO VINCENT'S ANGINA

An attack of Vincent's angina does not appear to give protection against subsequent attacks. An individual's response to this infection is largely by means of phagocytois and the local destruction of the organisms, and without treatment infections with the Vincent's microorganisms are apt to be long drawn out.

THE CLINICAL MANIFESTATIONS OF VINCENT'S ANGINA

Nothing is known about the incubation period It presumably is a matter of a few days only, because it is a local infection at the point of entry.

The onset of symptoms is usually quite sudden with marked pain in the throat, difficulty in swallowing, and fever, which

in some cases may be as much as 103° F. In the extensive cases, there are usually great prostration and toxemia, probably due to the presence of a secondary infection, but in the mild cases the constitutional manifestations are often astonishingly slight in contrast to the appearance of the pharynx. The breath usually is very foul, and pain is almost always severe, so that swallowing becomes very difficult and the problem of maintaining the patient's nutrition may become a matter of considerable importance. A secondary cervical lymphadenitis may be slight or marked.

The examination of the throat at first reveals one or more deposits of a thick false membrane on the tonsils or soft palate This becomes thicker and rather granular in character so that it can be removed with a swab more easily than a diphtheritic exudate The process in the severe cases causes marked ulceration and erosion of the tissue, and it is not uncommon to see the greater part either of a tonsil or of the uvula eaten away. This ulceration is more or less characteristic. When the superficial slough is wiped away, a deep sharply-defined ulcer may be found with irregular overhanging edges but with relatively little surrounding inflammation. When the lesion is of the lateral wall of the pharynx, there is grave danger of erosion into a blood-vessel, resulting in fatal hemorrhage. The color of the exudate or false membrane is occasionally greenish, but in some cases it is very similar to that of diphtheria, in fact the appearance of the lesions in many cases of Vincent's angina may resemble diphtheria so closely that the differentiation can be made only by bacteriological means

There is usually no anemia. The leukocytes are not often markedly increased unless there is a secondary infection, but the lymphocytes are apt to show a relative increase Occasionally a blood count will reveal that an agranulocytosis is present, the fusospirochetosis being a terminal infection In the majority of cases of infectious mononucleosis, inflammation of the pharynx or mouth may be found, Vincent's organisms often being associated with these lesions

THE COMPLICATIONS OF VINCENT'S ANGINA

The complications are those of a secondary infection, *such as with a streptococcus or more rarely these days with* the diphtheria bacillus, in which case the condition is usually very severe. Ulceration into the blood-vessels may occur if the lesion is situated in the side wall of the pharynx.

THE DIFFERENTIAL DIAGNOSIS OF VINCENT'S ANGINA

1. *Diphtheria*.—The most important feature of Vincent's angina and the reason for its inclusion in this book, is the resemblance it bears to diphtheria. The two diseases may have almost identical clinical manifestations in the throat, except that the one yields to diphtheria antitoxin and the other does not. Vincent's infections are more inclined to ulcerate than are diphtheria infections, the odor is usually much worse, and pain is apt to be more severe. The diagnosis is based on an examination of smears to detect the presence of the Vincent's organisms, and on examination of cultures for diphtheria bacilli. In the days when diphtheria was a common infection, the two diseases not infrequently coexisted.

2. *Acute Tonsillitis*.—Vincent's angina may also be differentiated from acute tonsillitis by the presence in the former of lesions elsewhere than in the tonsillar crypts, by a lower blood count, and by the finding in smears of the specific microorganisms. In mild cases it also has much less fever and constitutional reaction.

3. *Herpangina due to Coxsackie Viruses*.—The clinical picture of this condition includes fever, sore throat, and inflammation of the pharynx with characteristic grayish white papules or vesicles on the fauces, and (less frequently) on the uvula, tonsils and soft palate. The vesicles, which are surrounded by an areola of intense redness, enlarge and evolve into small, shallow ulcers. The thick exudate of

Vincent's angina is absent, however, and smears of the involved areas do not contain the Vincent organisms

4. *Herpetic Stomatitis.*—This disease, due to herpes simplex virus, is common among children, those one to six years of age being most often affected. The illness is characterized by fever, irritability, swelling and inflammation of the gums, and a vesicular eruption of the buccal mucosa In some cases the tonsillar area is also extensively involved The vesicular lesions lose their covering to become ulcers Herpetic stomatitis differs from Vincent's infection in a number of ways The ulcers of herpes usually remain small, and there is little tendency to pseudo-membrane formation (unlike Vincent's disease). Herpes virus causes intense inflammation and swelling of the gums, but ulceration of the gums does not occur, in contrast with Vincent's infection Smears from the edge of a fresh herpes vesicle contain multinucleated giant cells which contain intranuclear inclusion bodies Herpes simplex virus can readily be recovered by injection of vesicle fluid into the rabbit cornea or into the brain of suckling mice (See Plate III opp pg 118)

5 *Tuberculous ulceration of the throat* may be similar in appearance to Vincent's angina, but is generally associated with tuberculosis of the lungs

6 *Mucous patches due to syphilis* are invariably painless, do not show definite ulceration, and are more superficial

7. *Other conditions* such as scurvy and mercurial stomatitis must be considered, and the possibility of an underlying condition such as agranulocytosis, or leukemia must be eliminated

THE PROGNOSIS OF VINCENT'S ANGINA

In uncomplicated cases, the infection usually responds slowly but completely to treatment, but the occasional loss of tissue from the uvula, from the faucial pillars, or from the tonsils is permanent Very rarely death may result from secondary infection, or from erosion of a blood vessel

PERIOD OF INFECTIVITY OF VINCENT'S ANGINA

Patients with Vincent's infections should be isolated until all clinical evidences of the disease have disappeared and smears have been found negative for the organisms. In most communities there are no quarantine regulations for this infection.

PROPHYLAXIS IN VINCENT'S ANGINA

The mouth should be kept in as good condition as possible because Vincent's spirilli are probably pathogenic for man only when either local or general resistance is low. Inflamed gums and carious teeth should be treated, and tonsils with evidences of chronic infection should be removed. A tooth powder consisting of

Sodium perborate	ʒ vj
Precipitated calcium carbonate	ʒ ij
Powdered castile soap	gr xxx
Saccharin	gr j
Oil wintergreen	gtt x
Oil peppermint	gtt j

is not only pleasant and effective in keeping the teeth clean, but is also beneficial for the gums and curative of slight Vincent's infections in the mouth. Soap has a definitely spiricidal effect.

THE TREATMENT OF VINCENT'S ANGINA

The spirillum of Vincent's infections being very susceptible to penicillin the administration of this antibiotic by any one of a number of methods will give very rapid cures. Parenterally-injected penicillin is secreted in the saliva. Aqueous procaine penicillin, given by intramuscular injection is the

most effective. Six hundred thousand units are given at 12-hour intervals for the first two doses, after this, 600,000 units are injected once daily for the next three days Preparations of penicillin suitable for oral use are also effective and may be used instead of injectable penicillin. Tablets of buffered potassium penicillin G, tablets or suspension of Bicillin or of penicillin V may be used (see page 72) The dosage for penicillin given by mouth is 200,000 to 300,000 units, four times daily, for four days Penicillin troches and lozenges are also used by some physicians for the treatment of Vincent's infection, but we do not recommend this form of therapy because it appears to be more likely to cause sensitivity to penicillin than when this antibiotic is given parenterally or orally.

Within forty-eight hours, penicillin will almost invariably clear up all symptoms of fever, pain, malaise, and foul breath. The spirilli and most of the fusiform bacilli will disappear from the smears in the same period but the local lesions take several days longer to heal

The tetracycline drugs, and chloramphenicol are also curative in Vincent's angina, although they are not as effective as penicillin They should be used, however, when the patient is known to be sensitive to penicillin The tetracyclines are given in a dose of 25 to 40 mgm per kilogram of body weight per day, and chloramphenicol is used in 40 to 50 mgm per kilogram doses daily

During an acute Vincent's infection either of the throat or mouth, nothing should be done which might irritate the soft tissues such as brushing the teeth, but after the acute infection has subsided all possible breeding places of the microörganisms in pockets in the teeth or tonsils should be cleaned out.

Gargles with peroxide or sodium perborate are helpful High doses of vitamin C, nicotinic acid, and thiamin chloride have been advocated as adjuvants, but there is no evidence that they are of value.

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6

Streptococcal Infections

BETA HEMOLYTIC STREPTOCOCCAL INFECTIONS OF THE RESPIRATORY TRACT, INCLUDING SCARLET FEVER

Synonyms.—Streptococcosis, streptococcal fever, (scarlatina is a synonym for scarlet fever)

Definition.—Infection of the upper respiratory tract by beta hemolytic streptococci which cause local inflammation usually of the pharynx and tonsils, with a tendency to spread to adjacent structures such as lymph nodes, middle ear, and sinuses. In addition to the local inflammatory process, systemic symptoms such as fever, malaise, headache and vomiting are present. When the infecting streptococcus produces an erythrogenic exotoxin, and the patient does not possess specific antibody against this toxin, a skin eruption occurs (scarlet fever).

In some cases the initial illness is followed, after a latent interval, by nephritis, rheumatic fever or erythema nodosum.

Exciting Cause.—The great majority (over 90 per cent) of beta hemolytic streptococcal infections of man are caused by streptococci which are members of Lancefield Group A. These are the organisms which correspond to the "Str. pyogenes" of the earlier literature. A small percentage of streptococcal respiratory infections are caused by Group C and Group G strains. Division of streptococci into groups is based upon their production of group-specific carbohydrates (C substance). Each group specific C carbohydrate precipitates with its corresponding specific antiserum, but not with serum produced with C carbohydrate from other

groups. Groups A, B, C, D, and E were described by Lancefield in 1933. Later, groups F, G, H, K, L, M, N and O were identified.

Group A streptococci contain two antigenic proteins, the M and T proteins which are type specific. The M proteins are now used as the basis of the type classification of these organisms. Group A streptococci have been divided, by means of precipitin reactions with anti-M serum, into more than forty specific serologic types. In many of these serologic types the M and T antigens both are unique for that particular type. Others of the types contain their own type-specific M substance, but the T antigens present are closely related to T antigens elaborated by other types.

The type specific M protein is closely associated with the virulence of group A streptococci, and antibodies produced against M protein in animals are closely related to type specific protective action of immune sera. Animals inoculated with streptococci containing a specific type of M protein become immune to streptococci of the homologous type, but not against heterologous types. Specific anti-M antibodies appear in the sera of human beings within three weeks after infection, and persist as long as three years. Grouping and typing of streptococci are of importance in studying the epidemiology of streptococcal infections. Also, it may be of practical value to determine whether or not type 12 is present, since infection with this organism is much more liable to be followed by nephritis than is the case with any other type.

Several products of group A hemolytic streptococci are of some practical importance in the diagnosis, prognosis and treatment of streptococcal infections and their sequelæ such as rheumatic fever. They include streptokinase, streptodornase, two hemolysins, hyaluronidase, and erythrogenic toxin.

Streptokinase, or fibrinolysin, is produced by strains of group A streptococci, and some strains of group C and group G. Streptokinase acts catalytically with plasminogen,

a proenzyme present as an inactive proteolytic factor in all human serum, to form a proteolytic enzyme called plasmin which actively digests fibrin and other proteins. This mechanism brings about the lysis of a fibrin clot by streptococcal filtrates as described by Tillett and Garner in 1933 Streptokinase may assist the spread of streptococci through tissues by causing lysis of fibrin barriers. Infection with a streptococcus which produces streptokinase brings about the production of an antibody, antistreptokinase, which inhibits the action of streptokinase Sera of immunized animals and of human beings who have recently recovered from a streptococcal infection therefore prevent the solution of a fibrin clot by the streptococcal filtrate. Complete inhibition of a clot (*i e.*, a high concentration of antistreptokinase in a patient's serum) indicates a recent hemolytic streptococcal infection The diagnostic value of such an observation in rheumatic fever or nephritis is apparent. However, absence of antistreptokinase does not necessarily exclude a streptococcal infection, since some strains are poor producers of streptokinase, and there is considerable individual variation in antibody production among patients.

Streptodornase is an enzyme product of streptococci It is a desoxyribonuclease (DNASE) which splits desoxyribonucleoprotein and desoxyribonucleic acid into simpler polynucleotides. Antibodies against streptodornase occur in the sera of patients convalescent from group A streptococcal infections Antistreptodornase appears in fewer than half such patients, and generally the titer reached is not very high. McCarty found that on the average, patients who developed post-scarlet fever rheumatic disease had a greater anti-streptodornase titer than those whose convalescence was uneventful

Group A streptococci produce two *hemolysins* which disrupt red blood cells. These have been labelled streptolysin S and streptolysin O (oxygen labile), the latter being the more important. Streptolysin O is produced by most group A strains and by some group C and group G streptococci as

well. Infection of humans with these streptococci causes the production of antibody (antistreptolysin O) which combines quantitatively with streptolysin O, and prevents hemolysis of erythrocytes. The presence of a high titer of antistreptolysin O in a patient's serum, or an increasing titer over a period of several weeks is indicative of a recent streptococcal infection. Seventy-five to 90 per cent of patients who have recently undergone a group A streptococcal infection develop demonstrable antistreptolysin O, which may persist for many months.

Hyaluronidase, an enzyme which splits hyaluronic acid, is formed by many strains of streptococci of the group A variety, as well as those of most other groups. Hyaluronidase, by reducing the viscosity of hyaluronic acid in the tissues, might aid in the spread of the streptococci, thus enhancing their virulence. However, no definite correlation between hyaluronidase production and virulence has been established for group A streptococci. Infection of humans with group A streptococci which produce hyaluronidase is followed by the appearance of an antibody, antihyaluronidase in the serum. This antibody neutralizes the action of hyaluronidase. Newborn infants have a serum hyaluronidase concentration equal to that of their mothers, but this disappears within six months. The antibody begins to re-appear in children three to five years of age, and increases until early adult life is reached, after which it remains at a constant level. This sequence of infants is regarded as being related to experiences with group A streptococcal infections with increasing age. As described below, a similar sequence occurs with erythrogenic antitoxin production.

Erythrogenic toxin is produced by over 90 per cent of group A streptococci, and by a few group C and by a very small number of group G strains. The erythrogenic toxin produced by different strains of group A streptococci differ qualitatively, and it appears that at least five erythrogenic toxins exist. The presence or absence of antitoxin against erythrogenic toxin is determined by the Dick test (described

in detail on page 172), a positive reaction indicating that no antitoxin is present. Newborn infants give a negative Dick test, but this picture changes rapidly and by four months of age, 25 per cent of infants are positive, and by one year of age, nearly 80 per cent are positive. After two years of age, a steady fall in the percentage of Dick positive reactions occurs, being approximately 50 per cent at five years, 30 per cent at nine years, 20 per cent at twelve years, and 10 per cent at eighteen years, and remains between 5 and 10 per cent at older age levels. The lack of newborn positive reactors is explained in the main by the transplacental transfer of maternal antitoxin, and the change to positive, in the first few months of life is due to a loss of this antitoxin. The subsequent gradual change back to Dick negativity probably corresponds with increasing contact of the population, as it ages, with group A streptococci which produce erythrogenic toxins There is some evidence, however, that the Dick negativity of newborns may be due in part at least to the fact that the skin of the newborn infant may be incapable of reacting to erythrogenic toxin A newborn may give a negative Dick reaction even if his serum contains no antitoxin

EPIDEMIOLOGY

The ability to group and type streptococci has contributed greatly to the understanding of the epidemiology of streptococcal infections Our knowledge of this subject has been clarified by numerous studies carried out during the past 18 years Notable among these are the observations made by Schwentker and co-workers in Roumania from 1936 to 1939, and those of a number of groups of investigators in the armed services during World War II.

The streptococcal flora of a community in non-epidemic times is made up of many different types, at times including nearly all known types The prevalence of individual types varies greatly, some types are rarely encountered, while

others may make up as much as 20 per cent of all streptococci obtained from healthy carriers. The makeup of the streptococcal population is, however, not a constant one, but is constantly changing. A rare type may within a few months spread through the community until it becomes one of the dominant strains, and remain so for a long period. Later it may decrease in frequency, being replaced by another type. There is a definite seasonal rhythm in the carrier rate, which roughly corresponds to a similar cycle of streptococcal infections The lowest rates are found during the summer months, after which they rise rapidly during late fall and winter, reaching a peak in March In general, carrier rates are higher among children than adults.

Streptococcal infections are common in temperate and cold climates, and rare in the tropic areas of the world. This fact is clear from the studies of the world-wide incidence of scarlet fever made by Schwentker. He found that most cases of scarlet fever occur in the areas lying between 30° and 60° north latitude, and 10° to 40° south latitude In the zone between 30° north and 10° south latitude the morbidity for scarlet fever is practically zero, but in the zones north and south of this band the disease rate increases by logarithmic proportion with the degree of latitude

In the United States the highest morbidity rate for streptococcal infections, including scarlet fever, is in the Rocky Mountain States, and in general the incidence is higher in the North than in the South.

The vast majority of streptococcal cases are due to contact with a human carrier, either sick, convalescent, or clinically well. It is probable also that air-borne infections account for a proportion of streptococcal infections. In the dry indoor air in winter, streptococci may be spread great distances by air currents. Shaking of sheets or stirring up the dust of a ward occupied by persons harboring streptococci greatly increases the number of streptococci in the air. Under such conditions there is great interchange of various types of streptococci, and late complications are usually due

to a new type rather than the one with which the patient entered the ward. More direct contact also plays a part in the spread of streptococcal disease, and hands contaminated with nasal discharges containing streptococci are probably an important source of infection. Serious epidemics due to contaminated milk have been reported on many occasions.

Those types of group A (and some group C and G) streptococci which elaborate erythrogenic toxin may cause scarlet fever as well as streptococcal pharyngitis and tonsillitis in persons who do not have antitoxic immunity. The capacity to produce scarlet fever is not limited to any particular type; strains representing all types of group A streptococci have been isolated from patients with this disease. However, during epidemics of scarlet fever, a single type may be responsible.

IMMUNITY TO STREPTOCOCCAL INFECTIONS

At least two forms of resistance against group A streptococci have been demonstrated. One of these is antibacterial immunity related to the type specific M protein component of these organisms, the other is antitoxic immunity against erythrogenic toxin.

Antibacterial Immunity.—Most clinical and laboratory data point to the importance of type specific antibacterial immunity. Patients infected with a given type of group A streptococcus develop antibodies against the type specific M substance of the infecting strain, but do not produce antibodies against M substance of any other type. These antibodies remain in the patient's sera for a number of years and it is very probable that resistance against infection with streptococci of this homologous type will persist for a long period. The maximal duration of this type specific immunity is not known. A number of observations support the belief that the antibacterial immunity against streptococci is mainly type specific. These include the observation that soldiers with bacteriostatic antibodies against a given

type of group A streptococcus did not experience nasopharyngitis due to that type, while their barrack-mates, without such antibodies did contract such infection. Similarly, patients with group A streptococcal infections do not possess (early in the course of illness) antibacterial antibodies against the homologous infection strain, but do possess such antibodies against heterologous strains. This fact probably means that the antibodies which they do possess have resulted from prior infections with types different from that causing the current infection. Also on many occasions it has been noted that patients with infection due to one type of streptococcus have during convalescence suffered a second infection due to another type, but no instance of a repeated infection with a single type has been reported Indirect evidence on this point is also furnished by the fact that many adults have anti-M antibodies against various group A streptococci, while young children (three to five years of age) have few or none probably due to the fact that they have experienced fewer streptococcal infections by far than have the adults

Since antibacterial immunity to group A streptococci is so largely type specific, it follows that an individual may experience many streptococcal infections each due to a different type However, no individual suffers infections with each one of the more than 40 different types of group A streptococci, a fact which points to the existence of some non-specific factors in the pattern of streptococcal immunity This partial resistance to types which are different from those which previously caused infection may be dependent upon the development of immunity against substances which are common to all group A streptococci This hypothesis is supported by the observation, repeatedly made during streptococcal epidemics in the armed forces, that recent recruits exposed to highly invasive strains of group A streptococci became infected more rapidly than troops who have had several months or years of living in crowded barracks.

Antitoxic Immunity.—Antitoxin against erythrogenic toxin may be present in the blood as a result of previous infection with erythrogenic toxin-producing strains of group A streptococci, or as a result of transplacental passage In the latter case, the antitoxin disappears rapidly and is practically never found after one year of age. However, if the antitoxin has been acquired as a result of infection (clinical or sub-clinical) with erythrogenic toxin-producing group A streptococci, it will usually remain present throughout life Antitoxic immunity can also be induced by injection of erythrogenic toxin. Immunity against erythrogenic toxin prevents the occurrence of the rash of scarlet fever, but it does not protect against infection of the pharynx and other tissues by group A streptococci. For example, a person whose serum contains antitoxin but no antibacterial immunity against type 12 group A streptococci, will not develop scarlet fever when infected with this organism, but he may develop streptococcal pharyngitis Thus, the immune status of an individual may fall into a number of categories in relation to a given type of erythrogenic toxin-producing group A streptococcus.

1 He may have specific antibacterial immunity against the particular type of invading streptococcus as well as antitoxic immunity against the erythrogenic toxin

2 He may possess specific antibacterial immunity, but he may have no antitoxic immunity

A person in either category 1 or 2 will not develop stretpococcal pharyngitis or scarlet fever when he comes into contact with this organism

3 He may have no specific antibacterial immunity, but may have *antitoxic immunity. Such a person may suffer an* attack of streptococcal pharyngitis as a result of the invasion of the streptococcus in question, but he will not have scarlet fever

4. He may have neither antibacterial nor antitoxic immunity, in this case he will develop scarlet fever (strepto-

type of group A streptococcus did not experience nasopharyngitis due to that type, while their barrack-mates, without such antibodies did contract such infection. Similarly, patients with group A streptococcal infections do not possess (early in the course of illness) antibacterial antibodies against the homologous infection strain, but do possess such antibodies against heterologous strains This fact probably means that the antibodies which they do possess have resulted from prior infections with types different from that causing the current infection Also on many occasions it has been noted that patients with infection due to one type of streptococcus have during convalescence suffered a second infection due to another type, but no instance of a repeated infection with a single type has been reported Indirect evidence on this point is also furnished by the fact that many adults have anti-M antibodies against various group A streptococci, while young children (three to five years of age) have few or none probably due to the fact that they have experienced fewer streptococcal infections by far than have the adults

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capacity, and is probably the result of successive exposure to many different serologic types of streptococci (Swift)

The full effect of streptococcal infection is produced by erythrogenic toxin-producing organisms upon individuals who do not possess type specific antibacterial antibody sufficient to prevent the infection or antitoxin to neutralize the effects of the toxin. **Scarlet fever** represents this complete disease. For this reason, the bulk of the remainder of this chapter is devoted to a description of this particular form of streptococcal respiratory tract infection It should be borne in mind, however, that the local inflammation, the invasion of tissues at the portal of entry which is usually the pharynx, and the sequelæ are the same whether or not a rash is present, and the group A streptococci are the etiologic agents in both types of the illness

The two Drs. Dick of Chicago in 1923-1924 were the first to satisfy Koch's postulates, proving that specific hemolytic streptococci were the cause of scarlet fever. By means of human volunteers, they were able to reproduce the disease with organisms isolated from scarlet fever patients. They grew the organisms in broth, and in the sterile filtrate of this broth demonstrated the presence of a toxin which, if injected intracutaneously in small quantities furnishes a test showing immunity or susceptibility to the toxic manifestations of the disease, and which also if injected in sufficient doses causes these typical manifestations. These effects of the toxin are neutralized by incubation with the serum of convalescent patients. The toxin in small doses may also be used for the immunization of persons and horses, the blood serum developing antitoxic properties. Others, notably Dochez, had previously demonstrated the specific toxin, and Dochez had also previously advanced the hypothesis that scarlet fever was an infection of the upper respiratory tract or some other tissue with a specific streptococcus, and that the rash and other lesions were due to the action of the toxin

coccal pharyngitis plus rash) when invaded by the streptococcus under discussion

General Characteristics of Streptococcal Respiratory Infections.—The age of the patient, in a general way, determines the type of clinical response to infection with group A streptococci Powers and Boisvert state that in infants under six months of age streptococcal respiratory infection *is generally accompanied by irregular fever, and moderate* inflammation of the mucosa of the nasopharynx. The acute episode, in the untreated infant lasts about one week, and is followed by persistent nasal discharge, and some indisposition for about six weeks In children six months to three years of age the onset is less abrupt, and the systemic symptoms are subacute, with low-grade fever which continues for four to eight weeks The evidences of inflammation of the pharynx is not intense Spread to lymph nodes and middle ear is common, but low-grade systemic symptoms are usually the striking feature of the disease, with the local inflammation *a less prominent feature In children under three years of* age, scarlet fever is unusual, and tonsillitis is uncommon Sequelæ such as nephritis and acute rheumatic fever are rare in this age group In children over three years of age, and in young adults, the disease tends to be *progressively* more abrupt in onset, and more acute in its course. Local inflammation becomes more striking with increasing age of the individual affected, and tonsillitis is progressively more common The frequency of scarlet fever also increases after the age of three years, reaching its peak among children eight or nine years old, and then declining. The incidence *of nephritis rises reaching its peak among older* children and adolescents. Rheumatic fever begins to appear among children over three years of age, and its incidence rises steadily until it reaches its maximal incidence (for first attacks) among children *ten to fourteen years old.*

The changing response to streptococcal infection with advancing age has been termed a "returning" of reactive

omitted because there being only a minimal amount of protein in the material, pseudo-reactions are rare. The Dick test is ordinarily positive the first one to three days in scarlet fever, and usually becomes negative in one to two weeks or more from the beginning of the disease; it may already be negative even though done the day of the onset of the fever, or in a few cases it may remain positive throughout the illness, not changing to a definite negative until the fifth or sixth week if then. A swing from positive to negative in the course of an illness is diagnostic of scarlet fever. A negative Dick test indicates antitoxic immunity only, and it is not uncommon for a person with a negative test to have a throat *infection due to scarlatinal streptococci, but without a rash* and the other toxic evidences of scarlet fever.

The Dick reaction is suppressed in possibly 10 per cent of cases of measles, poliomyelitis, varicella, and whooping cough. This suppression is apparently not accompanied by an increase in the circulating antitoxin but is due to a decrease in the skin sensitivity.

In the vast majority of cases of scarlet fever, the *portal of entry* of the causative group A streptococcus is the pharynx, but scarlet fever may also result from infection of the puerperal tract, of surgical and other wounds, of burns, or of the skin of patients with eczema. It is of interest that even in such instances, the streptococcus is often found in the pharynx as well as in the wound or in the burned tissue, a fact which suggests direct auto-inoculation or hematogenous spread to the injured area.

To a considerable extent scarlet fever is a cold-weather disease, there being about twice as many cases in New York City in winter as in summer, with the peak usually in March. Although scarlet fever may occur in warm climates, there is a fairly well-recognized tropical insusceptibility. Negroes, the Yellow Race, and Eskimos are relatively immune. Some families exhibit at times a marked susceptibility. The incidence in males is slightly higher than in females up to six years of age, after which age the proportion is reversed. The

All types of group A streptococci contain members which produce erythrogenic toxin, and are capable of producing scarlet fever. Some strains of group C and group G streptococci also have this capacity, and a small percentage of cases of scarlet fever are due to these organisms. A few strains of Staphylococcus aureus also elaborate an erythrogenic toxin, and, rarely cause a disease clinically indistinguishable from streptococcal scarlet fever.

The Dick Test.—The Dick test for susceptibility or immunity to the toxin of scarlet fever was introduced in 1924. It consists of an intracutaneous injection of 0.1 ml of a standardized dilution of the erythrogenic toxin produced by various beta-hemolytic streptococci. This dilution is standardized by means of skin tests made with various dilutions in susceptible human beings so that the result of the injection will be a uniform reaction. The amount of toxin used in the injection is considered one *skin-test dose* (S.T.D., see page 601). Susceptibility to the erythrogenic toxin of scarlet fever-producing streptococci is shown by reddish discoloration and reaction at the point of injection appearing in from eight to twelve hours, and disappearing in three days or less. To be judged accurately the Dick test should be observed between eighteen and twenty-four hours after the injection. It should be considered positive if at the examination in a bright light there is even a slight redness or flushing of an area 10 mm. (⅜-inch) or more in diameter at the site of injection. However, marked redness may be found in an area 3 to 5 cm. in diameter. These differences in the intensity and size of the skin reactions correspond to differences in degree of susceptibility, and partly explain the great variation in severity of the toxic manifestation of scarlet fever. The technic of the test should be exact: the syringes and needles should be sterilized only by boiling in distilled water, and the 0.1 ml. injected should be accurately measured. The reaction is much less marked and much shorter in duration than that of the Schick test, and is not usually followed by a brownish stain, induration, or desquamation. A control test with heated toxin is ordinarily

THE PATHOLOGY OF SCARLET FEVER

Death during scarlet fever is usually the result of septic complications which, therefore, determine the variations in the pathological findings. After death the eruption usually fades away entirely, except where hyperpigmented, so that at autopsy, unless there is still evidence of the acute pharyngitis, the only gross abnormal finding may be a soft swollen spleen and enlarged regional lymph nodes. Microscopically, in many organs may be found an interstitial infiltration with mononuclear cells (Brody and Smith). The heart in a large proportion of cases shows interstitial infiltration, usually mononuclear but occasionally with some admixture of polymorphonuclears. The infiltrates may not be related to blood-vessels, or they may accumulate around and in the walls of small coronary arteries (arteritis and periarteritis) or beneath the endothelium of thebesian veins. In the liver the interstitial infiltration is present usually in the portal areas; in the spleen it is beneath the endothelium of trabecular veins. In the kidneys the interstitial infiltration begins around the veins situated between the cortex and medulla and spreads into the cortex, it may be so severe as to suggest the kidney lesions in leukemia (Fig. 19). In addition there is usually interstitial edema, congestion and tubular degeneration. Glomerulitis is only rarely found at autopsy before the third or fourth week of the disease. The urinary abnormalities may be very slight despite the rather marked pathological changes and consist in slight albuminuria and red and white blood cells in the urine.

Although blood cultures taken just before death or at autopsy usually are positive for hemolytic streptococci, the microorganisms are practically never seen in sections of the viscera, the visceral lesions being considered by some authorities toxic manifestations, by others allergic. The latter factor is especially favored as the cause of the glomerular nephritis of scarlet fever, which occurs usually after two or

disease may occur at any age but is commonest between four and ten years, nearly one-half of all the cases occurring in that age period Infants usually have a congenital immunity that clinically lasts ten months or more, so that scarlet fever is quite unusual during the first year. When it does occur then, it is generally serious. Skin tests have shown that more than one-half the children tested during the second six months of life are susceptible to the toxin; also that not more than 25 per cent of adults are susceptible, although by the age of twenty years only 10 per cent have had recognizable scarlet fever.

Natural Immunity —The relative immunity of Negroes, Eskimos, and the Yellow Race is apparently a natural immunity, and various Caucasian families appear to be relatively more immune than others. Also there seem to be certain individual variabilities, as yet little understood, whereby some people remain immune through several exposures and then become susceptible and contract the disease at a subsequent exposure. The state of immunity and of sensitization passes through variable periods and thus there are times when the appearance of scarlet fever is an accident occuring during a period in which the immunity appears to have diminished.

In the last fifty years scarlet fever has become increasingly benign and while epidemics of the infection continue without much diminution in the number of reported cases, the mortality rate has dropped very markedly. For instance in New York City in the five years from 1900 to 1904 there were 59,651 reported cases with 4,152 deaths, and a mortality rate of six in a hundred cases while from 1940 to 1944 the figures are 45,777 cases and 49 deaths or only slightly more than one death in a thousand cases. In 1954 only 2,143 cases were reported to the Department of Health, and only one death was recorded The extremely great decrease in the number of reported cases is due, in part, to the fact that the disease is no longer considered by many physicians to be worth reporting (See Table 8, page 278)

three weeks of the disease, and thus rather late for a toxic manifestation.

In surgical scarlet fever, the local lesion shows congestion and purulent infiltration or necrosis of the skin and underlying tissues with numerous streptococci in the inflamed area.

Blood.—A moderate polymorphonuclear leukocytosis is usual, and there may be a slight increase in the number of eosinophiles.

THE CLINICAL MANIFESTATIONS OF SCARLET FEVER

The *incubation period* of scarlet fever is one to seven days usually two to four Longer periods from exposure to the onset of symptoms have been reported, but are unusual

The symptoms may best be divided into three groups: (1) those due to the primary infection at the point of entry, usually the pharynx; that is, the sore throat. (2) The toxic manifestations or those due to absorption of the toxin. These include fever, vomiting, the exanthem, the strawberry tongue, a mild general lymphadenitis, possible headache or delirium, and in markedly toxic cases myocarditis or nephritis. Multiple arthritis may be a toxic manifestation in some instances but in many it is a rheumatic infection activated by the scarlet fever. (3) Septic manifestations or those due to invasion by the streptococcus or by some secondary invader These include fever, particularly of the septic type, the more severe forms of pharyngitis with membrane formation, cervical adenitis, otitis media, rhinitis, and sinusitis, also septicemia, pyelitis or pyelonephritis, endocarditis, etc.

1. Early Manifestations.—The onset of scarlet fever is usually sudden. It is characterized by a triad of symptoms—fever, sore throat, and vomiting.

The *fever* as a rule rises abruptly to an average height of 102° or 103° F., reaching this maximum on the second or third day and returning gradually to normal by the end of the first week in cases not treated with serum. (See page 44). In mild cases the fever may not go above 101° F, and in



FIG 18 —Photomicrograph of a section of the heart in scarlet fever showing the arteritis (*A*) and the cellular perivascular infiltration (*B*).

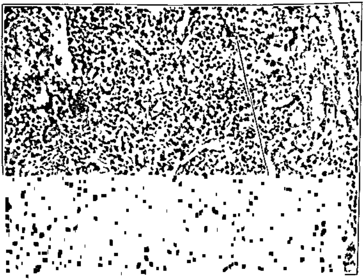


FIG. 19 —Photomicrograph of a section of a kidney in scarlet fever, showing diffuse interstitial infiltration (*A*), also congestion and cellular proliferation of two glomeruli (*B*).

is observed in scarlet fever much more frequently than in measles, but it is not so characteristic a feature as it is in diphtheria. Convulsions are apt to usher in the disease in infants of the spasmophilic type

2. **The Fastigium and Convalescence** — *The Exanthem.*— In scarlet fever the eruption on the skin, while quite variable in its extent and severity, is fairly constant in its outstanding features. In cases of average severity the rash ordinarily has enough characteristic features to make a diagnosis comparatively easy, but in mild cases so many of these details may be absent as to make a positive diagnosis quite difficult.

A typical eruption will show most of the following features: It begins to appear in from twelve to forty-eight hours after the onset of the fever, reaches a maximum in one to two days, and fades out in from three to seven days, usually five. The rash is a general erythema or hyperemia of the skin, with a superimposed punctate congestion of the skin papillæ and hair follicles giving the appearance of fine, red goose-flesh on a red background. To the touch of the examining hand, the skin feels hot but dry The eruption fades on pressure except when hyperpigmented Hyperpigmentation even to the extent of multiple tiny petechial hemorrhages is apt to occur extensively in severe toxic cases especially in blonds, also in the creases of the folds of the joints, notably on the flexor surface of the elbow. Accordingly in most cases of scarlet fever, even when the eruption is quite mild, transverse lines which do not fade on pressure are found at the elbow (Pastia's sign). Miliary sudamina or tiny blebs, pin-head in size, and containing a colorless drop of fluid, are occasionally found in considerable number when the rash is severe, and notably across the chest Stroking an area of marked eruption as with the edge of a tongue depressor causes immediate blanching of the line, followed at once by the disappearance of the blanching, in turn followed in about a minute by a second blanching of the line, lasting possibly an additional minute. This dermographia is quite marked in most true cases but is occasionally also obtained in the toxic erythemas

very severe cases a temperature of 104° F. or more may be maintained for several days In these severe toxic cases there also is apt to be considerable sepsis and the fever assumes a septic type, the return to normal depending on the course of the sepsis.

The *sore throat* of scarlet fever is characterized by pain of average severity, although in mild cases the patient may hardly notice the involvement of the pharynx. On examination the mucous membrane across the vault of the soft palate and on the posterior pharyngeal wall is at first found to be diffusely congested with closely scattered bright red spots. In a few hours the pharynx becomes beefy red, edematous and wet in appearance, two or three small petechiæ may be found, and there may be small scattered spots of a greenish-gray mucoid exudate suggesting drops of pus rather than pseudomembrane In mild cases the pharynx may appear merely slightly red, while in very severe cases there may be pseudomembrane formation, ulceration, and even gangrene. The appearance of the throat in diphtheria may be closely simulated. In other words, there is the customary picture of a "streptococcus sore throat" of more or less severity, *except that in addition there is the red eruption in the* mucous membrane of the palate, the so-called enanthem, which is a toxic manifestation superimposed on the bacterial pharyngitis

Vomiting, the third feature of the triad, occurs once or twice during the first six to twelve hours in about three-fifths of the cases. Occasionally there is nausea without vomiting.

Other features of the onset of scarlet fever are quite variable. Headache, malaise, and general prostration are quite marked in some patients. A mild general lymphadenitis is usually found if looked for, the inguinal chains in particular being almost invariably palpable during the first few days of the disease. In rare cases there may be a prodromal eruption consisting of a diffuse erythema appearing on the face and body for perhaps a day. The pulse-rate is often found to be more rapid than the amount of fever would indicate. This

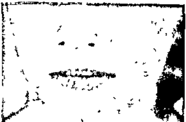
PLATE IV



A



B



C

due to other infections, such as influenza. The typical exanthem of scarlet fever is apt to appear first in the areas of warmth and pressure, such as the folds of the skin over the joints, the groin, the buttocks, and the small of the back in bed patients, and over the sternum and between the shoulder blades. It spreads rapidly, involving the entire body below the chin-ear line. It characteristically does not involve the face except in severe toxic cases, when it may be found to a slight degree on the temples and below the eyes. The cheeks are notably flushed but the rest of the face is usually quite pale, particularly the triangle from the nose to the chin. As a result, circumoral pallor is a characteristic feature which is present in a majority of cases The eruption may become fainter when the circulation is poor or when the patient is cold It may sometimes be brought out more strongly by wrapping the patient warmly in blankets. In negroes the rash appears more commonly on the face than in white people and is often visible only there and in the palms of the hands and the soles of the feet, but tiny punctate swellings may be made out in the skin of the body and extremities. There may be a marked burning sensation but actual itching is usually slight Edema and swelling of the skin, especially of the face, can occasionally be found at the height of the rash.

An extensive rash and a high fever usually predicate a massive infection at the portal of entry, usually the throat, but a severe septic throat condition in scarlet fever does not necessitate an extensive rash In fact, in patients infected

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LEGEND FOR PLATE IV
Scarlet Fever

A Showing an extensive eruption on the abdomen with a positive blanching reaction near the umbilicus
(From the collection of L H Koplik, M D)

B. Showing the enanthem on the uvula and palate, the swollen wet uvula and tonsils, and (out of focus) the heavy coat on the dark red tongue
(From the collection of H A. Towsley, M D)

C. Showing the flushed cheeks and circumoral pallor, and the eruption on the neck.
(From the collection of L. H Koplik, M D)

by erythrogenic toxin-producing streptococci, there may be any degree of exanthem, from one of maximum severity to none

If 0 1 to 0 2 ml of a diluted serum (either horse or human) containing antitoxin against erythrogenic toxin of beta hemolytic streptococci is injected intracutaneously, where the eruption is marked, blanching at the site of injection will occur in from eight to twelve hours and in the majority of cases will last for the duration of the eruption. This is probably due to the specific local effect of the antitoxin on the toxin It is known as the *Schultz-Charlton* or blanching reaction (first described in 1918) While a positive blanching test may be considered pathognomonic of scarlet fever, a negative test while militating against a diagnosis of scarlet fever, may mean merely that the case being tested is due to some unusual strain of the scarlatinal streptococcus This reaction may be used for diagnosing an uncertain eruption with a known scarlatinal antitoxic serum, and also for testing an undetermined antitoxin by means of its effect on a known scarlatinal eruption The serum used for this injection should be diluted with 50 to 100 parts of sterile normal saline to avoid the confusing effects due to the injection of an undiluted serum A positive Schultz-Charlton reaction is more apt to be obtainable in new or early rashes than in those that have been present three days, and it can very rarely be obtained on or after the fourth day of a rash A positive blanching test may be contemporary with either a positive or a negative Dick test If a horse-serum antitoxin is used for the test, serum reactions will occur in isolated instances, and also a degree of sensitization may develop On the other hand, injection of human serum carries the risk of transmission of serum hepatitis The Schultz-Charlton test should therefore be done only when a clear need for it is present In most instances, the recovery of beta hemolytic streptococci from the throat of a patient with a rash which resembles that of scarlet fever is sufficient to establish the [illegible]

Pseudo blanching phenomena may occur. Thus an eruption may spare an area of skin at the site of a previous injection of vaccine or serum, or in the neighborhood of a pre-existing skin infection and along the lymphatics running from that infection. Occasionally, a non-scarlatinal rash may be blanched by the injection of human serum if it contains suitable antibodies.

Scarlet fever has an even greater effect in depressing or neutralizing a tuberculin skin reaction than has measles so that a negative tuberculin test obtained during the acute stage of scarlet fever cannot be accepted as evidence that the person does not normally give a positive reaction.

A *general desquamation* usually follows the exanthem involving the entire surface of the skin including the face, and in general is proportionate to the intensity of the rash which preceded it. Desquamation usually begins during the second week of the disease and lasts two to three weeks or longer. It begins where the rash began or where the skin is thinnest and ends where the skin is thickest, as in the calluses of the palms and soles. Desquamation from the face is usually in fine branny flakes, and may be found as early as the fifth day of the disease; from the body and extremities it is usually also in rather fine pieces, though rather characteristically in confluent circles; but from the hands and the feet it may be in large flakes or even as a thick cast involving the

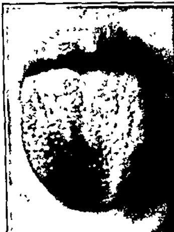


FIG. 22. — So-called "strawberry tongue," showing the enlargement of the lingual papillæ. (Schamberg and Kolmer, Acute Infectious Diseases.)

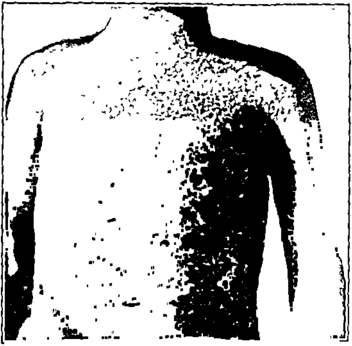


FIG. 20.—Unusually severe desquamation in a case of scarlet fever with an intense eruption (Schamberg and Kolmer, Acute Infectious Diseases.)



FIG. 21.—Desquamation in scarlet fever on the sixteenth day. (Howard Fox, Archives of Dermatology and Syphilology.)

ears are all involved and pour forth a foul-smelling blood-tinged, putrid discharge, and where the cervical glands are massively swollen and the prognosis almost hopeless, even from the start. Similarly, epidemics vary, and in the years gone by, a busy practitioner might see no fatal case for twenty years or more and then meet an epidemic where one patient in four died. In New York City in 1882 the mortality of 10,560 cases was 28 per cent, but it is hoped that with the specific remedies available today there will be no more such veritable plagues due to scarlet fever and that deaths due to this disease will remain as at present a rarity.

Surgical Scarlet Fever.—The focus of infection is occasionally at other points of the body than the fauces—as for instance in wounds operative or otherwise, in burns, or in the puerperal uterus. These cases reveal the usual toxic manifestations of scarlet fever such as fever, vomiting, strawberry tongue, and a typical exanthem However, there is no inflammation of the pharynx, but rather a septic condition at some other point from which the scarlatinal streptococci can be cultured Such cases are usually called surgical scarlet fever. Group A streptococci are often present in the throats of patients with surgical scarlet fever, a fact which suggests that the infection of the burn or wound may, at times, be a secondary one

Surgical scarlet fever may also follow operations on the mouth, nose, and throat (Lovett) The wound in these cases is in the region most likely to harbor streptococci and corresponds to the portal of entry for non-surgical or ordinary scarlet fever The interval between the operation (whether it be for cleft palate, diseased tonsils, adenoids, etc) and the first symptoms of the disease is usually two to four days, and most of these cases are of the septic type with an unusual number of complications, and poor operative results. Particularly when scarlet fever is abundant, culturing and immunizing patients before such nose and mouth operations are advisable.

skin of the entire palm and fingers. A very characteristic and almost diagnostic feature is desquamation of the skin of the finger-tips. In addition the nails may develop wrinkles or may appear dead with a fairly sharp line of demarcation appearing later between the old nail and the newly-developing fresh nail tissue.

The *tongue* with its rather characteristic appearance provides another feature of the fastigium. The first day or two of the disease the tongue becomes coated with a marked gray or brown fur, then swollen papillæ appear and peep up through the coat, particularly along the margin of the tongue The coat then desquamates so that by the fourth or fifth day the tongue may be beefy red with a number of swollen papillæ dotted on it, especially toward the sides and tip. The term "strawberry tongue" is usually applied to this clinical feature which appears in nearly one-half the cases of scarlet fever. A somewhat similar but less marked appearance is occasionally also found in other diseases, particularly measles In fact, no one feature of the exanthem or of the tongue is pathognomonic of scarlet fever with the exception of a positive Schultz-Charlton blanching reaction

Additional features of the fastigium and early part of convalescence include a sensitiveness to heat and cold, occasional headaches or delirium, which may be marked in severe cases, and a secondary anemia. Early in scarlet fever the blood will usually show a polymorphonuclear leukocytosis with a moderate eosinophilia appearing during desquamation Paresthesias are not uncommon. Of greater importance at this stage of the disease, however, is the tendency to secondary infection, or to further invasion by the scarlatinal streptococcus itself.

Thus, cases of scarlet fever are markedly diversified—from very mild ones difficult to diagnose, with little or no rash, to the overwhelming malignantly toxic cases of sudden terrific onset and death in one or two days' time; from cases with only a slight redness of the pharynx and little fever, to those extensive septic conditions where the throat, nose, and

period. Acute glomerular nephritis, and rheumatic fever are the most important sequelæ of streptococcal infections

COMPLICATIONS

1 **Rhinitis and Sinusitis.**—Rhinitis is not part of uncomplicated scarlet fever but indicates the spread of the infection—or of a secondary infection—from the pharynx to the nasopharynx and rhines, and probably also to the facial sinuses, so that a nasal discharge is of great importance in being an obvious clinical evidence of the presence of an invasive infection Of the sinuses, the ethmoids are involved in an unusually large proportion of cases, the diagnosis being commonly made by roentgen-ray

2. **Cervical Adenitis.**—Cervical adenitis of sufficient degree to be called a complication is quite common, occurring in 10 to 15 per cent of all untreated cases. While slight swelling of the cervical lymph nodes is found in the majority of cases of scarlet fever during the first day or two of the disease, marked swelling denoting a complication occurs in connection with practically all severe throat involvements It occasionally goes on to abscess formation, and more rarely it may be accompanied by a diffuse cellulitis of the neck, called Ludwig's angina Occasionally also, an otherwise uneventful convalescence is interrupted in the third or fourth weeks by a moderate fever and a rather protracted cervical adenitis

3. **Otitis Media.**—Otitis media is the third common complication of scarlet fever, occurring particularly in very young patients. Without antibiotic therapy from 10 to 13 per cent of large series of cases of scarlet fever have developed otitis media of which 25 to 50 per cent were bilateral, mostly in little children The symptoms and signs are usually typical The severity of otitis media varies greatly In some instances only slight reddening of the drum, which subsides spontaneously, is observed In other instances, the eardrum becomes seriously involved in a very short time re-

Relapses and Recurrences.—Following possibly 1 per cent of cases of scarlet fever (the mild ones or those treated only a short time with antibiotics, or particularly those with persistently positive Dick tests) *relapses may occur from three* to six weeks after the onset of the original attack, or recurrences of the disease at a still later period. The new attacks may be milder or more severe than the original one and, though auto-reinfection is considered possible, are usually due to a new infection with a different strain of the scarlatinal streptococcus. Convalescent cases with persistently positive Dick tests should accordingly be kept separate from other convalescing scarlet fever patients.

COMPLICATIONS AND SEQUELÆ OF STREPTOCOCCAL INFECTIONS INCLUDING SCARLET FEVER

The manifestations of acute streptococcal diseases may be divided into three groups: primary illness, complications and sequelæ.

1. The primary illness is due to the immediate infection, which we have already described.

2. Complications are caused by spread of the streptococci from the original site of infection to adjacent tissues. Complications usually begin during the second week after onset of the primary symptoms. Rhinitis, sinusitis, cervical adenitis, otitis media, mastoiditis, peritonsillar abscess, and septicemia are among the septic complications which may occur.

3. Sequelæ are manifestations of disease caused by alterations in the affected organs induced by soluble substances elaborated by the streptococci at the site of the primary infection. Sequelæ may represent a hypersensitivity reaction to group A streptococci. Sequelæ usually make their appearance three weeks or longer after onset of the primary streptococcal infection. They do not follow immediately after the end of the primary illness, but after a latent or quiescent

abscess; toxic psychoses and encephalitis (but any affection of the central nervous system is relatively rare in scarlet fever); also enteritis in infants; and other infectious diseases, particularly diphtheria Acute mesenteric lymphadenitis may be mistaken for acute appendicitis and an idiopathic peritonitis has also been described complicating scarlet fever. Pneumonia, while occasionally met (1.5 per cent of hospital cases), is not nearly so common as in measles or diphtheria. The larynx is rarely involved in scarlet fever unless due to a complicating secondary infection as with the diphtheria bacillus The pseudomembranous infections of the throat that are found early in the septic cases are in the majority of instances caused by a streptococcus, those found during the convalescence of scarlet fever are usually due to the diphtheria bacillus.

SEQUELÆ

1 *Acute Glomerular Nephritis.*—As in most acute infectious diseases, albuminuria is frequent during the early stages of scarlet fever. In addition, by means of addis counts, Lyttle has shown that from two to four weeks after onset of disease nearly all patients with streptococcal infection excrete in the urine more albumin, blood cells and casts than normal persons The incidence of definite acute glomerular nephritis is fortunately much lower. Before the introduction of sulfonamides and penicillin, acute glomerular nephritis occurred in, in our experience, in 2 to 3 per cent of patients with scarlet fever More recently this incidence has fallen to approximately 0 5 per cent, probably as a result of treatment with antibiotics. The incidence of nephritis varies with the type of streptococcus causing the primary illness. Among the group A streptococci, type 12 is by far the most liable to cause nephritis

It is probable that all cases of acute glomerular nephritis are preceded by beta-hemolytic streptococcal infections, although some of these may be so slight as to be missed clinically.

sulting in purulent otitis media. Pain in the ears, fever, and other systemic manifestations occur rapidly In about one-fourth of the cases of untreated otitis media mastoiditis may occur Further spread of infection may cause thrombosis of the lateral sinus, abscess of the brain, and meningitis Impairment of hearing following otitis media in scarlet fever used to be all too common, but penicillin and other antibiotics has materially decreased the incidence and likelihood of this unpleasant sequel.

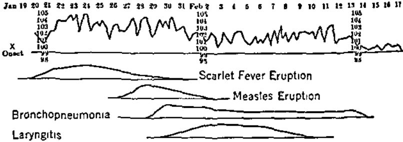


FIG 23 —Showing the presence together in a boy, aged four years, of measles and scarlet fever, with complications, in the days before specific therapy was available (Arch. Pediatrics.)

4 **Septicemia** —*In contagious disease hospitals,* presence of the hemolytic streptococcus in the blood of scarlet fever patients is not very rare, either during the active stage of the disease itself or later in the presence of other complications At times a persistent moderate fever and perhaps some petechiæ are the only clinical manifestations of the bacteriemia More commonly, however, a definite septicemia is present and is responsible for a protracted septic type of fever, general toxicity, and either death or a long delayed and stormy convalescence.

5 **Other Complications** —Other complications of scarlet fever include septic pharyngitis and quinsy or peritonsillar

(0.3 per cent) with group A streptococcal infections who were treated with penicillin, while 17 cases occurred among 800 untreated controls (2 per cent) Recurrences of acute rheumatic fever are extremely common among those who have experienced a previous attack of the disease, when they contract a new streptococcal infection

Symptoms and signs of rheumatic fever usually appear in the third week after onset of a streptococcal infection, but sometimes they are delayed as much as six or seven weeks. Occasionally rheumatic fever begins within ten days after the initial streptococcal disease The patient with a typical attack develops a relatively high fever (102° F to 104° F.) One or more joints become painful, tender to touch, and swollen The arthritis, which is non-purulent, is migratory involving first one joint and then another Knees, ankles, wrists, elbows and shoulders are most often involved, but the joints of the fingers and other small joints may also be affected In severe cases subcutaneous nodules may appear over the extensor surfaces of wrists, elbows, ankles and over the skull Usually the pulse rate is rapid, and in many patients pericarditis, endocarditis and myocarditis occur, and can be detected by clinical and laboratory means The mitral and aortic valves are usually affected by the endocarditis, the other valves escaping injury In general the more severe the systemic symptoms the more likely is cardiac involvement but this is not always true The disease varies greatly in its severity, being extremely intense, stormy, and prostrating in some instances, while in others the patient feels so well that he is able to carry on with his usual activities Between these extremes all degrees of severity are encountered It is interesting that post-streptococcal nephritis rarely occurs in conjunction with rheumatic fever

There is usually a well marked polymorphonuclear leukocytosis, with a total white blood cell count ranging from 12,000 to 35,000 per cubic millimeter The erythrocyte sedimentation rate is greatly elevated, ranging from 25 to nearly 100 millimeters per hour.

Glomerular nephritis usually occurs eighteen to twenty-one days after onset of the primary streptococcal infection, but it may occur as early as the fourteenth and as late as the thirty-sixth day. Onset may be abrupt, with fever, passage of bloody urine, oliguria, edema, azotemia, elevation of blood pressure, and convulsions. On the other hand, the disease may be very mild, with only slight oliguria and only microscopic evidence of abnormal kidney function. In the severe cases evidence of myocarditis may be found on physical examination and by the electrocardiogram. In nearly all cases the sedimentation rate is elevated. The duration of acute glomerular nephritis is also very variable. In some instances all evidence of the disease disappears within a week, while in other cases both clinical and laboratory evidences of abnormal kidney function persist for several months. In general, however, the prognosis is excellent. The vast majority of patients recover completely and chronic nephritis rarely follows the acute glomerular nephritis of scarlet fever.

2. *Rheumatic Fever.*—This is the most serious sequel of streptococcal infections, because of its tendency to cause permanent injury to the heart. The exact pathogenesis of rheumatic fever is not yet entirely clear, but it is certain that it is always preceded by an infection with group A hemolytic streptococci. In many cases the streptococcal infection may be so mild that it escapes clinical recognition. In such instances, however, it is possible to show the presence of a significant titer of antibodies against some antigenic component of group A streptococci, such as streptolysin O. Rheumatic fever is very rare in children under three years of age. After this age it increases in incidence, reaching a peak at twelve or thirteen. In general 3 to 5 per cent of children with untreated group A streptococcal infection develop acute rheumatic fever. This incidence can be greatly reduced by treatment with penicillin given promptly and for a sufficient length of time. For example, Denny showed that only 2 cases of rheumatic fever occurred [illegible]

tions. Failure to obtain improvement within forty-eight hours with penicillin may be regarded as indicating that one is not dealing with a streptococcal infection

THE DIFFERENTIAL DIAGNOSIS OF SCARLET FEVER

1. *Rubella.*—In this disease the exanthem is usually pinker, and changes character each twenty-four hours; it is apt to look like measles the first day, like scarlet fever the second day, and be gone the third day. The face is as much involved as is the body, and the rash is more speckled and less of a confluent erythema than is that of scarlet fever The skin is more apt to be moist and clammy than in measles or scarlet fever The exanthem of rubella is accompanied by disproportionately slight constitutional symptoms; usually there is little fever and no appreciable sore throat, though the pharynx may appear slightly congested and also speckled Swelling and tenderness of the posterior cervical lymph nodes are characteristic, but the anterior cervical lymph nodes are ordinarily not notably enlarged In rubella there may be a distinct increase of lymphocytes (See page 254)

2 *Measles* —Here there is much more rhinitis and conjunctivitis and a different type of fever curve, and the rash is usually much more macular. Between the macules the skin is not erythematous. Koplik's spots are to be found, and in the eyes the caruncle and the plica are congested The rash is marked on the face, where it precedes the rash on the body There may be a prodromal rash in measles quite suggestive of scarlet fever, but its duration is short The tongue also may cause confusion, occasionally being quite similar to the strawberry type (See page 230)

3 *Toxic rashes and erythemas,* occur in various infections such as influenza, typhus fever, and sepsis especially due to infection with toxin-producing staphylococci These usually involve the entire body, including the face Dermographia, Pastia's sign, and desquamation are all much less common

The acute phase of an untreated bout of rheumatic fever usually lasts from four to six weeks, but often laboratory evidences of continuing activity may be obtained for months after all clinical signs have disappeared. Furthermore, there is a great tendency for recurrence of the rheumatic process following streptococcal infections, and each of these causes increasing myocardial and endocardial damage. The result of such repeated attacks is chronic cardiac disease

In the older literature on scarlet fever the occurrence of "scarlatinal arthritis" is described This arthritis was believed to be different from the arthritis of rheumatic fever in a number of particulars It seems probable that most, if not all, of these cases represent mild bouts of rheumatic fever in which cardiac involvement did not occur, or was so mild as to escape clinical recognition

DIFFERENTIAL DIAGNOSIS OF STREPTOCOCCAL INFECTION WITHOUT A RASH

It is not possible to make a certain diagnosis of streptococcal respiratory infection without a rash unless bacteriologic studies are carried out. However, streptococcal infections generally cause more severe symptoms of illness than do those caused by such organisms as pneumococci and Hemophilus influenzæ Thus, fever is generally higher in streptococcal infections, and severe malaise and prostration are more common The local inflammation caused by streptococci is generally more intense, and the presence of exudate on tonsils and pharynx usually indicates infection with these organisms. Upper respiratory infections caused by viruses are also difficult to distinguish from those due to streptococci, and often such a differentiation cannot be made on clinical grounds Infection with the recently described adenoido-pharyngeal conjunctival viruses (which cause pharyngo-conjunctival fever) can be distinguished by the fact that they cause non-purulent conjunctivitis in over half the cases, while this finding is unusual in streptococcal infec-

breaks it was as low as 1 per cent At the present time in the United States the mortality from this type of streptococcal infection is well below 1 per cent. For example, only one death from scarlet fever was recorded in New York City in 1954 This improvement in the prognosis of streptococcal disease is undoubtedly due to the use of antibiotics in the treatment of these infections The mortality due to post-streptococcal rheumatic fever and nephritis is more difficult to estimate. It does seem to be clear, however, that the over-all incidence of rheumatic fever has been greatly reduced by antibiotic therapy

PERIOD OF INFECTIVITY OF STREPTOCOCCAL INFECTIONS

Patients are most contagious during the period of acute infection, which is approximately during the first week of disease However, group A streptococci are still present in the pharynx of approximately 25 per cent of untreated patients after the second week of illness, in 5 per cent after the third week, and in 1 per cent after the fourth week An individual is able to transmit infection as long as streptococci are present Patients are probably contagious several hours before the onset of symptoms

Group A streptococci spread rapidly from patient to patient, and under conditions of military life, the introduction of a given type of streptococcus may be followed by infection (although not necessarily by illness) of all the members of a barracks Under conditions of civilian life, the contagiousness of streptococcal infections is much more limited Streptococci spread more readily during the winter than during the summer It has been shown that children from four to eleven years of age are more apt to infect those about them than are adults or infants

ISOLATION AND QUARANTINE

In many cities and states, the reportable disease "scarlet fever" is now included in a wider classification, namely,

than in scarlet fever The Schultz-Charlton blanching test is negative, and the Dick test will not change from positive to negative in the course of the disease.

4. *Serum Rash.*—This frequently takes the form of a pure erythema suggestive of scarlet fever and even accompanied by fever There is usually some urticarial element, however, as well as a history of serum injection

5. *Drug Rashes*—Belladonna, copaiba, digitalis, ephedrine, phenobarbital, phenyl-ethyl-hydantrin, quinine, the salicylates, and especially the sulfonamides may cause eruptions in sensitive people quite similar to the usual eruption of scarlet fever

6 *Sunburn,* and erythemas due to other counterirritants.

7. *Skin diseases,* notably dermatitis exfoliativa, where desquamation occurs with the erythema rather than afterward.

8 *Heat Rashes of Infancy*—Here there may or may not be fever but there is no pharyngeal involvement and the rash is usually more macular, at least in certain areas.

THE MORTALITY AND PROGNOSIS OF STREPTOCOCCAL INFECTIONS

Death from streptococcal infections may be due to septic complications caused by spread of the organisms into the blood, mastoid cells, meninges and other organs, or from the sequelæ, nephritis and rheumatic fever The incidence of septic complications is greatly reduced by prompt administration of an effective anti-streptococcic drug, penicillin being the most effective Similarly, the early administration of penicillin in adequate doses and for a period of seven to ten days greatly reduces the occurrence of rheumatic fever, and probably also of nephritis These considerations apply for both streptococcic infections without a rash and for scarlet fever. Before effective antibiotic therapy was available, the mortality rate among patients with scarlet fever was as high as 15 to 40 per cent in virulent epidemics, while in other out-

matic fever, and glomerulonephritis Secondary infections with a new type of streptococcus, and recrudescence of the original infection are both prevented by maintaining an effective anti-streptococcal level of penicillin in the blood for a period of ten days. Such therapy also reduces the danger of the occurrence of rheumatic fever and nephritis to a minimum

Penicillin is best administered by intramuscular injection, a method which insures a satisfactory blood concentration Intramuscular injection of an aqueous suspension of procaine penicillin, 300,000 to 600,000 units once daily for ten days is probably the most effective form of therapy. However, the inconvenience and pain involved in this course of treatment make it necessary to use some alternative form of therapy in many cases For example, we have frequently given three daily injections of procaine penicillin, followed by seven days of an oral preparation of penicillin Some physicians use orally administered penicillin only, giving 200,000 to 300,000 units four times daily for ten days For this purpose tablets of potassium penicillin G or of Bicillin (dibenzylethylenediamine penicillin G) or penicillin V (phenoxymethyl penicillin) may be used For oral administration to small children, liquid preparations of the latter two drugs are available which contain 300,000 units per teaspoonful

As an alternative form of therapy a repository or depot preparation of penicillin may be used A single intramuscular injection of Bicillin, 600,000 units for children, or 900,000 units for adults, provides (in the great majority of cases) an effective anti-streptococcic concentration of penicillin in the blood for ten days, and is effective in curing the symptoms of the disease Furthermore, it quickly eliminates the streptococci from the pharynx, suppresses the formation of antistreptolysin, and is effective in reducing the incidence of rheumatic fever and nephritis The pain at the site of injection of Bicillin is often intense and persistent, and diminishes the usefulness of this preparation to some extent. Procaine penicillin with 2 per cent aluminum monostearate in peanut

"streptococcal sore throat, including scarlet fever," and for uncomplicated cases the isolation period is until the mucous membranes of the nose and throat appear normal, but not for less than seven days after the onset of the disease. Where there are complications such as a discharging nose or ears, enlarged or suppurating glands, pneumonia, etc, isolation is until recovery from the complications has taken place

Patients treated with penicillin for the recommended period of ten days are very rarely carriers of streptococci at the end of this period. There is therefore no need to exclude children so treated from school if they are clinically well, at the end of their course of therapy The desquamating skin of the patient with scarlet fever contains no streptococci. There is, of course, no reason to prolong the isolation period until desquamation has been completed

Contacts are no longer quarantined, because quarantine measures do not materially lessen the carrier rate of group A streptococci in the community The practice of many physicians of giving antibiotics to intimate contacts as a prophylactic also reduces the need for quarantine measures

TREATMENT OF STREPTOCOCCAL INFECTIONS

1. *Antibiotic Therapy* —Penicillin is the drug of choice for treatment of all streptococcal infections including scarlet fever, and it should be employed in every case unless the patient has previously suffered a reaction to it Penicillin is effective against all types of group A streptococci, and extremely few strains have been found to be resistant to it Streptococcal infections respond as well to penicillin therapy today as they did when this antibiotic was first introduced Administration of penicillin causes a prompt subsidence of the signs and symptoms of the primary infection and very rapidly eliminates the streptococci from the site of infection. It interferes with the production of streptococcal antibodies such as antistreptolysin. These two effects seem to be connected with the effectiveness of penicillin in preventing rheu-

2. *General Measures* —The patient should be kept in bed until he is clinically well, and if possible, until his course of antibiotic therapy has been completed This is just as necessary for a patient with streptococcal infection without a rash as it is for one with scarlet fever Fluids should be given freely as long as fever is present, the diet should be liquid in the first day or two of illness, and then gradually restored to a regular one, containing the usual amount of protein Older persons may be given gargles or irrigations with warm saline, but these procedures are usually not worth attempting for young children

The ear drums and heart should be examined at frequent intervals, and an electrocardiogram should be obtained at least once during the second and third week after onset of the primary disease Evidences of rheumatic fever should be looked for until six weeks have elapsed since the beginning of illness Urinalyses should be carried out every two or three days during the first two weeks after onset, and daily from the fourteenth to twenty-first day. The itching and burning sensation of the skin of the scarlet fever patient may be relieved by application of soothing ointments

3 *Serum Therapy* —Both human convalescent serum and antitoxin made from the serum of horses injected with erythrogenic toxin were formerly used in the treatment of scarlet fever The human serum probably contained antibacterial antibodies as well as antitoxin, but in view of the existence of 40 different types of group A streptococci, it is probable that whatever effect this type of serum had must have been due chiefly to its antitoxin content The effectiveness of the horse serum antitoxin was certainly dependent upon this factor Injection of antitoxin is followed by blanching of the scarlet fever rash, and the duration of fever and other toxic symptoms were usually shortened as compared with controls However, since the serum was antitoxic only, it was difficult to demonstrate an appreciable degree of prevention of septic complications, and its effect upon the incidence of rheumatic fever and nephritis was not

oil also has been used extensively, and appears to be equally effective. It is given intramuscularly, 600,000 for adults being injected every third day for three doses, with half as much for children This preparation, since it contains an oil which may act as an adjuvant, is probably more liable than the other preparations mentioned to bring about sensitization to penicillin

When penicillin cannot be used because the patient is sensitive to it, one of the tetracycline drugs should be used. Oxytetracycline (Terramycin) or tetracycline (Achromycin, Tetracyn, etc) in a daily dose of 25 to 40 milligrams of body weight, in four divided doses are given by mouth, this regimen should be continued for ten days The tetracycline drugs are quite effective in relieving the fever and other symptoms of the primary phase of streptococcal infections They probably approach penicillin in their ability to prevent the septic complications which are the result of spread of streptococci from the pharynx to adjacent tissues However, they are not so effective in destroying the streptococci at the primary site of infection, and in suppressing the rise of antistreptolysin titer in the patient's blood Probably correlated with these last two points is the fact that the tetracyclines do not prevent rheumatic fever and nephritis nearly so efficiently as penicillin does It is for this reason that the tetracycline drugs should only be used if sensitivity to penicillin prevents its use

The sulfonamides should be used for treatment of streptococcal infections only if penicillin or the tetracyclines cannot be used for some reason (such as sensitivity) which prohibit their use. In the first place, a considerable number of strains of group A streptococci are quite resistant to these drugs In addition, even when the sulfonamides relieve the symptoms of the acute phase of the infection, they frequently fail to destroy the streptococci in the pharynx, and do not prevent a sharp rise in the serum antistreptolysin titer. Perhaps because of this, they are not very effective in lowering the incidence of rheumatic fever and nephritis

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striking. Since penicillin is so effective in every way in the treatment of streptococcal infections, it is not believed that either horse serum antitoxin or human convalescent serum should now be used in the treatment of scarlet fever

4. *Prevention and Treatment of Complications and Sequelæ.*—Complications and sequelæ are best prevented by prompt treatment with penicillin, in dosage described above, for a period of ten days Probably rest in bed decreases the likelihood of complications, if only by decreasing the danger of a new infection with a different type of streptococcus

Otitis Media, Sinusitis, and Cervical Adenitis.—While the patient is on penicillin therapy the danger of streptococcal otitis media, mastoiditis and sinusitis is small. The occurence of these complications should bring to mind the possibility of secondary infection with penicillin resistant bacteria such as staphylococci, or Gram-negative rods of the Enterobacteriaceæ family, or Hemophilus influenzæ. Attempts to isolate these organisms from the nasopharynx and pharynx should be made, and treatment with erythromycin, or chloromycetin, or one of the tetracycline drugs should be instituted

There is some difference of opinion regarding the treatment of purulent otitis media We do not recommend incision of the drum, generally, unless 48 hours of antibiotic therapy has been tried Discharging ears should be kept clean so that drainage may be as free as possible. This may be accomplished in some patients by the frequent use of sterile swabs only, but when the discharge is thick and tenacious, occasional saline irrigations are indicated. When the discharge persists bacteriologic studies should be made to determine the bacteria present, and suitable antibiotic treatment given If such treatment is ineffective, mastoidectomy may be necessary

Septic Conditions of the Pharynx.—These are usually more harmed than helped by swabbing or painting. On the other hand, hot irrigations with mild solutions of 0 85 per cent sodium chloride are often comforting. When a pseudomembranous exudate is present, diphtheria antitoxin should be

given at once, without waiting for the results of cultures

Rheumatic Fever.—Adequate, promptly instituted, penicillin therapy reduces the risk of a primary attack of rheumatic fever, and lessens the danger of a recurrence in a patient who has previously suffered a bout of this disease Once signs and symptoms of rheumatic fever are noted, therapy aimed at reducing possible cardiac damage should be started. In general, the patient should be kept in bed until all clinical and laboratory signs of activity of the rheumatic process have disappeared. This is usually a period of at least four to six weeks Activity should be kept at a minimum during the first few weeks, the patient not being permitted to sit up in bed, or to feed himself Aspirin therapy *or cortisone treatment should be started as soon as* the diagnosis is made For mild cases, aspirin may be used, but patients with severe systemic symptoms and those with evidence of serious or rapidly progressing cardiac disease should be treated with cortisone Aspirin is given in dosage of 30 milligrams per kilogram of body weight per day together with 5 milligrams of sodium bicarbonate per kilogram per day A concentration of blood salicylate of 20 to 25 milligrams per hundred ml of blood should be maintained until clinical and laboratory considerations indicate that rheumatic activity has stopped Cortisone is given by mouth in dosage of 60 milligrams five times daily for four weeks, and then reduced gradually until no cortisone is given by the end of the sixth week after onset Metacortin, 12 milligrams five times daily, may be given instead of cortisone

Acute Nephritis—The danger of this complication is also diminished by adequate penicillin therapy. There is no specific treatment for glomerulonephritis, but treatment is supportive, giving the kidney the maximal chance for recovery The patient is kept in bed until the urine becomes nearly normal and th

protein intake, but the sodium chloride intake is limited to 1 to 2 grams daily.

When oliguria is present, the fluid intake is limited to the quantity required to replace that lost in the urine, stools, sweat, insensible perspiration, and by respiration. As oliguria disappears the restriction of the fluid intake is removed. If hypertension is present to a dangerous degree, blood pressure is reduced by intramuscular or intravenous injection of magnesium sulfate. Hypertensive encephalopathy is also treated in this way and by administration of phenobarbital, chloroform or other anticonvulsant drug. Myocarditis and sometimes cardiac failure may occur in patients with nephritis. In the latter case digitalization may be a lifesaving measure.

PROPHYLAXIS AGAINST STREPTOCOCCAL INFECTIONS

Antibiotics.—Persons exposed to streptococcal infections may be protected very effectively by administration of penicillin. For this purpose, 200,000 units of penicillin given by mouth before breakfast and at bedtime are effective. Tablets of potassium penicillin G, or of Bicillin, or Bicillin suspension may be used. This treatment should be continued for one week after the end of the exposure. The same effect may be obtained by a single intramuscular injection of 600,000 units of Bicillin. The tetracycline drugs (10 mgm. per kilogram of body weight by mouth daily) may also be used, but they are less effective than penicillin. Sulfonamides in a dosage of 0.5 gram to 1.0 gram by mouth daily also decrease the risk of streptococcal infection after exposure, but they should be considered as being the third choice.

It is extremely important to prevent streptococcal infections in those who have experienced one or more attacks of rheumatic fever, since each successive acute rheumatic episode increases cardiac damage. For this reason such persons should be kept on prophylactic anti-streptococcal therapy continually, and for many years. Here again, penicillin is the drug of choice for reasons already given. The American

Heart Association recommends the following listed in order of preference

1. 200,000 units of a penicillin preparation (made for oral use) taken each morning before breakfast Tablets of potassium penicillin G, or of Bicillin, or a suspension of Bicillin may be used *OR* Intramuscular injection of 1,200,000 units of Bicillin once a month.
2. Sulfadiazine, or Gantrisin, 0 5 to 1 0 gram by mouth once a day

Active Immunity —There is no vaccine available which will provide effective antibacterial immunity against the various types of group A streptococci It is, however, possible to produce active immunity against the erythrogenic toxins of these organisms This may be accomplished by subcutaneous injection, at weekly intervals, of increasing quantities of toxin, beginning with 650 skin test doses, and giving successively 2,500, 10,000, 30,000 and 100,000 However, since the immunity produced is directed only against the erythrogenic toxin it would prevent the rash of scarlet fever, and not streptococcal disease without a rash For this reason and others it is not recommended at the present time

Passive Immunity —Antitoxic immunity may be obtained by injection of the serum of persons convalescent from scarlet fever or of horse serum antitoxin This procedure is not recommended for those exposed to scarlet fever since the antitoxin in these sera prevents only the rash of the streptococcal infection, while penicillin prevents the infection entirely

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7

Measles

Synonyms.—Morbilli and rubeola

Definition—A widely prevalent communicable disease, characterized by fever, cough, coryza and conjunctivitis, a typical eruption and Koplik's spots

THE ETIOLOGY OF MEASLES

Exciting Cause.—A filterable virus present during the catarrhal stage in the secretions of the upper respiratory tract and also in the blood Monkeys are susceptible to an experimental measles, which, however, only moderately resembles human measles

Anderson and Goldberger in 1911 were the first to do extensive experiments in transmitting measles to monkeys, and in 1921 and subsequently, Blake and Trask produced substantiated evidence to warrant the assumption that the active agent is a filterable virus which is found both in the circulating blood and in the secretions of the mucous membranes during the early stage of the disease Later Taniguchi and others have similarly transmitted measles to man Finchley, Stokes and Rake and their associates have grown the virus on chick-embryo tissues, and have thereby apparently attenuated the virus so that on subsequent intranasal and intradermal inoculation of susceptible children they have produced a mild or modified measles but, unfortunately, without much protective value

In 1954, Enders and Peebles grew the measles virus in human and monkey kidney cells in tissue culture and passaged it in series The measles virus produces eosinophilic intra-

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1, 2, 3 to 12 is the sequence of publication of certain of the articles

last half of the first year and during the second year. In recent years, infants are usually cured if they develop secondary infections and the rare deaths that occur in measles are apt to be due to such complications as encephalitis in older children.

Season, Sex, Race, etc.—There is usually much greater seasonal variation in the incidence of measles than is the case with diphtheria or scarlet fever. There is a marked increase with the start of cold weather, usually reaching a maximum in the northern hemisphere in March, April or May and falling suddenly in June to a low incidence in September. The disease, though not uncommon in the tropics, is especially endemic in all large cities in the temperate zone. In New York City, London, and other large cities, for the past two or three decades there have been biennial epidemics, usually with more than three times as many cases as occur in the intervening years, but with occasional "breakstep" years to change the epidemic years from odd to even or vice versa. Rural communities suffer less than do urban, but isolated communities that have been free from measles for a number of years develop marked susceptibility to the disease, and eventually suffer devastating epidemics. In Greenland in 1951, only five of 4,262 exposed persons failed to contract the disease.[1] Likewise country dwellers when brought together, as in army camps, prove unusually susceptible. In the United States Army camps in 1917 and 1918 there were 98,225 cases of measles complicated by pneumonia in 6,283 cases, and with 2,370 deaths. The sexes are equally susceptible.

THE PATHOLOGY OF MEASLES

In the prodromal stage of measles, from one to four days before the appearance of the exanthem, the characteristic pathological lesion is the appearance of multinucleated giant cells in the lymphoid tissue. These giant cells may be present

[1] J. A. M. A., 153, 581, 1953.

nuclear inclusion bodies and giant cell formation in the tissue culture cells. These authors also showed that neutralizing and complement-fixing antibodies against the virus appear in the blood of children convalescent from measles. The complement-fixing type of antibody is present as early as the seventh day after the rash appears and it persists for at least two months thereafter

The virus has been accidentally proved by transfusion to be present in the blood at least during the latter half of the incubation period. Its presence in the blood continues through the catarrhal period but it can rarely if ever be recovered from the blood of a measles patient more than seventy-two hours after the appearance of the rash. However, it has been recovered from the brain tissue of a fatal measles encephalitis case nine days after the onset of the rash.

Mode of Infection.—This is usually by direct contact through droplet infection with the patient during the stage of invasion, by direct contact with articles freshly soiled by the secretions of the nose and throat, or by human carrier such as a nurse or physician going from a measles to a chickenpox ward. Measles is very easily carried from bed to bed in a ward, or even from room to room in a building, but owing to the limited viability of the virus away from the patient, it is practically impossible for a third person to carry the measles infection through fresh air from one building to another

The magnitude and frequency of exposure have been shown to have an influence on the certainty and severity of infection.

Age.—Infants under four to five months of age whose mothers have had the disease are immune, but all other persons who have not already had the disease are extremely susceptible. Measles of the new-born has been reported but is rare. *In a city like New York about 50 per cent of the* cases occur during the school years from five to fourteen, 2 per cent in older people and 48 per cent in infants and preschool children Before the days of sulfonamides and antibiotics, from 90 to 95 per cent of the deaths occurred during the first four years, the mortality being highest during the



FIG 25.—Photomicrograph of section of lung in measles showing (A) bronchiole filled with purulent exudate, (B) peribronchial infiltration, (C) interstitial interalveolar infiltration

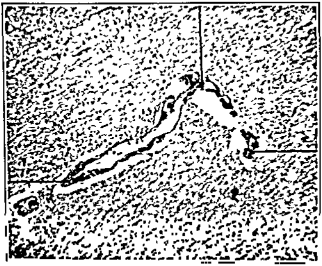


FIG 26 —Encephalitis in measles The wall of the blood-vessel is infiltrated with mononuclear cells (From the collection of Dr. Vera B. Dolgopol)

in and around the lymphoid follicles of the tonsils and of the appendix, which suggests why suppurative appendicitis is not uncommon towards the end of the incubation period of measles

In the stage of the exanthem there is found a small round-cell perivascular infiltration in the upper portion of the cutis with congestion and some edema This causes a general



FIG 24 —Measles Giant cells (*G*) in the pharyngeal mucosa (From the collection of Dr Vera B Dolgopol)

swelling of the skin, noticeable especially in the face. Small round-cell infiltration with congestion and some edema is also present in the mucous membranes of the eyes and of the entire respiratory tract. Koplik's spots are a manifestation of this infiltration, congestion, and necrosis occurring in the mucous membrane. *Denton found that a Koplik spot is an* inflammatory lesion of a submucous gland, and that the

IMMUNITY TO MEASLES

Passive Immunity.—Passive immunity is of two types If the mother has had measles, regardless of whether or not her baby is breast-fed, he receives a congenital immunity, which lasts from four to five months. Passive immunity may also be acquired by the injection of a specific human serum product, inducing thereby a temporary immunity lasting about four weeks. (See Prophylaxis, page 235.)

Active Immunity.—This may be acquired by an attack of the disease, either typical or modified An active immunity is almost invariably permanent in duration, though a few authentic instances of second attacks of measles have been reported, possibly due to an absence of gamma globulin, the store-house of antibodies, in the blood of these individuals

Measles may be modified by (1) the injection of a partially immunizing serum (to wit, a small amount of gamma globulin) into an exposed child during the incubation period, or (2) the inoculation of a susceptible child with virus attenuated by growth on chick-embryo tissue The first method of modification is now widely used, but is practical only when a child is known to have been exposed (See page 236) The second method involving actually infecting a child with modified virus is not practical, having not yet been proved sufficiently protective to be advocated

The presence of a natural immunity to measles is very unusual, and its occurrence is denied by many authorities

THE CLINICAL MANIFESTATIONS OF MEASLES

The symptoms of measles are quite variable in their duration, severity, and time relationship, particularly when adults are affected However, especially when the patients are young children, many cases run exactly true to type and many more run nearly so.

Four stages are usually recognized, separated by no sharp line of demarcation, but gradually merging. These are: (1)

bluish halo which is sometimes described about it, is due to the collar-like plexus of venules about the duct.

The inflammatory process is followed by desquamation of the superficial layers of the epithelium of both the skin and the mucous membranes. There is also a cellular hyperplasia in the lymphoid organs shown clinically by a slight general lymphadenitis and frequently also by a palpable spleen.

In the lungs in the febrile stage of the disease there is bronchitis with congestion of capillaries and a mononuclear interstitial peribronchial infiltration with edema and congestion resulting in thickening of the walls of the bronchi The bronchioles become filled with a purulent exudate, and the walls of the bronchioles and of the adjacent capillaries also become thickened and intensely cellular (Fig. 25). The result is many small areas of consolidation. When marked, these miliary-like peribronchial lesions grossly resemble in roentgen-ray examination, the tubercles of miliary tuberculosis. Secondary infection most commonly with a hemolytic streptococcus is often superimposed on this inflammation resulting in a patchy or confluent bronchopneumonia which is a common cause of death in measles A pneumococcus lobar pneumonia is not unusual, however.

When death has resulted from a measles encephalomyelitis, perivascular collections of lymphocytes may be found mainly in the white matter of the brain with proliferation of glial cells in the nerve tissue adjacent to the blood-vessels Usually there is also a perivascular loss of myelin, the waxy substance enveloping the nerve fibers

Blood.—During the incubation period of measles there is no significant change in the numbers of leukocytes in the blood but on the first day of fever there is a temporary fall in the number of lymphocytes followed in a day or two by a decrease in the number of *the other leukocytes resulting in* leukopenia with a predominance of lymphocytes. After the onset of the eruption a distinct leukocytosis indicates, as a rule, the presence of some complication, usually due to invasion by a secondary microörganism, notably a hemolytic streptococcus.

usually three to four days, with only very exceptional cases outside a one- to six-day limit.

In general, the features of this period may be most readily remembered by associating them with the fingers of the outspread hand. Beginning with the little finger is the first symptom, fever. About twelve hours later comes the ring finger or puffiness of the lower eyelid and some congestion of the caruncle and of the peripheral conjunctiva together with the first sign of the enanthem or rash in the throat

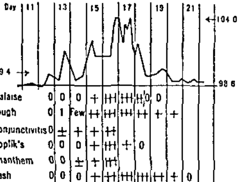


FIG 28 —Observations in a girl, aged eight years illustrating the priority of fever as a symptom (Courtesy of J A M A)

Approximately twelve hours later, or middle finger, come the evidences of catarrh, also known as the three C's, *viz*, conjunctivitis, coryza, and cough Another twelve hours later, or the forefinger, are found Koplik's spots Then thirty-six hours later, or as far from the forefinger to the thumb as it is from the little finger to the forefinger, comes the rash or exanthem, and for the palm of the hand we have a certain amount of headache and considerable malaise throughout this period

Fever.—In the great majority of cases this is the first evidence of ill-health to appear It usually falls into one of four more or less distinct types

Period of incubation, with a customary duration of nine or ten days; (2) period of invasion or prodromal stage of catarrh lasting usually three or four days; (3) period of eruption, or fastigium, lasting three to five days; (4) period of convalescence with desquamation.

I. **Period of Incubation.**—The average and customary time from a single exposure to the onset of the first symptom is ten days, with only rare cases falling outside the seven- to *fourteen-day limit. The duration varies with the virulence*

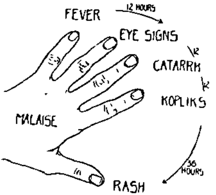


Fig 27.—The sequence of events during the period of invasion of measles (Courtesy of J A M A)

and dosage of the virus and the resistance of the patient, being shorter in the severe cases The giving of serum to an exposed child to modify the disease may lengthen the period to twelve, fourteen or even as long as nineteen days When the disease is transmitted by inoculation, as in a transfusion, the incubation period can be as short as seven days. During the incubation period there usually are no evidences of ill-health except that in England a "fever of infection" has been described.

II. **Period of Invasion or of Catarrh.**—This period is from the onset of the first evidence of ill-health, usually fever, to the onset of the exanthem or rash in the skin, and lasts

usually three to four days, with only very exceptional cases outside a one- to six-day limit.

In general, the features of this period may be most readily remembered by associating them with the fingers of the outspread hand. Beginning with the little finger is the first symptom, fever. About twelve hours later comes the ring finger or puffiness of the lower eyelid and some congestion of the caruncle and of the peripheral conjunctiva together with the first sign of the enanthem or rash in the throat

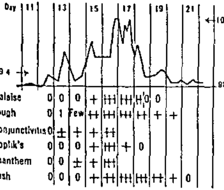


FIG 28 —Observations in a girl, aged eight years illustrating the priority of fever as a symptom (Courtesy of J A M A)

Approximately twelve hours later, or middle finger, come the evidences of catarrh, also known as the three C's, *viz*, conjunctivitis, coryza, and cough Another twelve hours later, or the forefinger, are found Koplik's spots Then thirty-six hours later, or as far from the forefinger to the thumb as it is from the little finger to the forefinger, comes the rash or exanthem; and for the palm of the hand we have a certain amount of headache and considerable malaise throughout this period.

Fever.—In the great majority of cases this is the first evidence of ill-health to appear It usually falls into one of four more or less distinct types

1. *The Typhoid Type.*—This is the usual type of rise, going up by daily increases in four to five days to a maximum of nearly 104° F at the time of the full bloom of the rash

2. *The Malarial Type*—In this type there appears a day or two of more or less fever with a return to normal or nearly normal for a few hours and then a quick rise in two or three days to the maximum with the eruption.

3 *The Pneumonic Type*—In the severe cases the fever is apt to rise quickly at the start to 103° F or more and hover around 104° to 105° F. until the rash has well appeared.

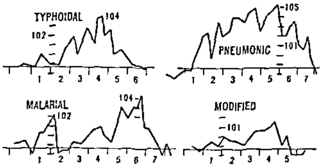


FIG 29—The usual forms of fever curve in uncomplicated measles, named according to the type of rise (Courtesy of J A M. A)

4 *The Modified Type*—This is found in cases which are made mild, either (1) by an inherited immunity which is fading out, as in infants of four to six months, or (2) by the administration of a specific serum, such as the blood of convalescent patients, in doses insufficient to afford complete protection but enough to mitigate the symptoms of the disease. Here the fever may not go over 101° or 102° F., and is comparatively gradual in rise and fall, and short in duration.

No matter what type of rise the fever may take, the fall is usually by crisis or rapid lysis, the temperature dropping very quickly to normal once the rash is well out. Should

it fail to do so, the presence of some complication should be presupposed and sought.

Eye Signs.—Following the onset of fever, the caruncle at the inner corner of the eye and the plica semilunaris become swollen, and occasionally there can be found thereon one or two small red macules with tiny elevated bluish-white spots, possibly similar in nature to the buccal spot, popularized by Koplik. (See later.) Meanwhile there may also be found a fairly definite line of beginning congestion across each lower

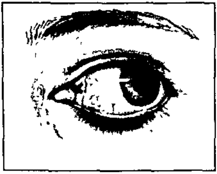


FIG. 30.—The inner corner of the eye at the height of the conjunctivitis showing the swollen caruncle and plica semilunaris with a macule on the latter.

eyelid, about at the margin of the tarsal cartilage and perhaps a third of the way from the lid margin to the fornix. This line is soon obscured by a more general conjunctivitis. There is apt to develop a seropurulent exudation with considerable photophobia (discomfort due to light), and the lids become slightly puffy. The conjunctivitis usually lasts until after the drop in temperature, and occasionally the eyes remain "weak" for some days into the period of convalescence.

Prodromal Rash.—Occasionally during the first day or two of the stage of invasion an eruption appears, particularly on the chest and neck. The rash may consist of many fine macules somewhat resembling the rose spots of typhoid

fever or the eruption of rubella, or it may be a blotchy erythema, or it may resemble quite closely the diffuse erythema of scarlet fever. In rare cases it may be somewhat urticarial in type. This eruption usually is very short lived, disappearing before the onset of the typical exanthem of measles. It is of importance, however, in obscuring an early diagnosis.

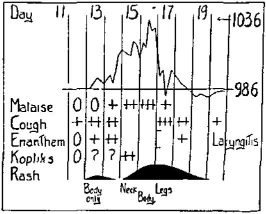


FIG. 31.—Observations in a woman, aged thirty-six years, illustrating non-conformity in an adult to the rule of priority of fever, also a prodromal rash This patient was the mother of the patient recorded in Fig 28 (Courtesy of J A M A)

The Enanthem.—Usually about the second day of fever there appears on the soft palate, the uvula, the tonsils or the posterior pharyngeal wall, a slight congestion together with a number of scattered reddish-brown spots, pin-head in size. This congestion becomes more marked and the spots themselves become more numerous and confluent, so that by the fourth or fifth day the pharynx may be markedly congested and irregularly brownish-red in color When the involvement of the pharynx is extensive numerous tiny opalescent miliary vesicles may be seen This enanthem usually lasts until the eruption on the skin is well marked and it fades as the temperature of uncomplicated cases returns to normal

Profuse involvement of the pharynx may be evidenced symptomatically by pain, especially on swallowing.

Catarrh —Because of the catarrhal involvement of the mucous membranes of the eyes, nose, larynx, trachea, and bronchi in the pathological process, there appear the clinical manifestations of conjunctivitis, coryza, and cough (the 3 C's).

The *conjunctivitis* becomes quite marked and the eyes as a whole look red, watery, and puffy. There may be enough seropurulent discharge to cause the lids to stick together.

The *coryza*, or nasal catarrh, is apt to be preceded by premonitory sneezing The usual manifestations of a nose cold become quite marked by the time the exanthem appears.

Tompkins[1] has found that prodromal measles can be simply and easily diagnosed by aspirating nasal mucus, spreading it on a slide, and staining the material with Wright's Stain The characteristic multinucleated giant cells which pathologists have long associated with measles, can be demonstrated in the nasal exudate (Also see Fig 24, page 210)

The *cough* of measles is a frequent, non-productive, tight, irritating, hacking cough due to the inflammation of the mucous membrane of the larynx and trachea. In addition, a certain amount of bronchitis is to be considered part of any case of measles rather than a complication At this stage the patient appears and feels quite woebegone.

All the manifestations of catarrh usually reach maximum severity about the end of the period of invasion when the fever is at its height and the exanthem is becoming apparent They usually clear up even more rapidly than they appear with the exception of the cough, which is apt to persist into convalescence.

Koplik's Spots —Although spots on the mucous membrane of the cheeks in measles had previously been described by various writers, Koplik, in 1896, was the first to attribute to them specific diagnostic importance, and as a result of his description the spots have since been called by his name.

[1] New York State J Med, 55, 2157, 1955

Koplik's spots comprise the first pathognomonic evidence of measles. When marked, these spots resemble grains of white pepper loosely sprinkled on a red background. They first appear usually on the second or third day of the disease as small, red patches, in the center of which is a tiny opalescent whitish speck much less than pin-head in size. They are usually first found in the mucous membrane on the inside of the cheek, about opposite the first molar teeth, but as they become more numerous they may be found all over the inside of the cheeks and in marked cases on the mucous membranes of the gums and lips They have also been reported in nasal and vaginal mucous membranes as well as on the inner caruncle of the eye When marked they are usually seen in any good light and the patient may speak of the mucous membrane of the cheek as feeling rough to the tongue When few in number, or fading, or just appearing, they are best seen in strong daylight and possibly are not seen at all by artificial light.

Koplik's spots are found when looked for in nearly every case of unmodified measles, and usually disappear as the exanthem becomes full blown. They are of especial importance because when they have been found a definite diagnosis of measles can be made and the child isolated, possibly two or three days before the appearance of the rash makes the disease self-evident Unfortunately, however, they do not *usually appear until the child already has been catarrhal* (and thereby markedly contagious) for an appreciable number of hours

Throughout the period of invasion the patient is apt to suffer also from a good deal of diffuse headache and general malaise, and drowsiness is fairly common. The spleen may be palpable.

III. **Period of Eruption, or Fastigium**

The Exanthem.—On the average the eruption of measles appears about fourteen days after the exposure, three to four days after the onset of fever, and thirty-six hours after the appearance of Koplik's spots. The eruption usually

PLATE V



Measles.

Showing the bleary eyes and puffy lids, and a full blown eruption.

(From the collection of L. H. Koplik, M.D.)



Measles.

Showing the upper teeth of one side, a slightly coated tongue and the inflamed mucous membrane inside a cheek with a number of Koplik spots.

(From the collection of H. A. Towsley, M.D.)

lasts about five days unless hyperpigmented, in which case the pigmentation may last one or two weeks.

The rash may first be found behind the ears or on the forehead or on the cheeks. It spreads down the body, on the first day being usually discrete on the face, on the second day somewhat confluent on the face and discrete on the trunk; on the third day confluent on the body and discrete on the arms and legs It fades in the order of appearance, the face usually being practically clear when the eruption is beginning to fade on the extremities.

The rash of measles, especially when involving the face, is usually accompanied by a certain amount of edema or puffiness, and the affected skin is apt to itch and burn.

The eruption begins as small, reddish-brown macules which may appear at first to be beneath the skin. The spots soon become papular and irregularly confluent, leaving areas of normal skin between the eruptive areas The eruption fades on pressure except when it is hyperpigmented Hyperpigmentation is apt to occur in severe cases, or in blondes, or in the creases of skin in average cases and is characterized by a purplish color with stippling, suggesting intracutaneous capillary hemorrhage Some brownish staining of the skin usually persists for a few days after the actual eruption has gone, the discolorations coinciding in size and shape with the original areas of eruption, and occasionally having some diagnostic value But in the hyperpigmented cases the staining is especially marked, resembling innumerable tiny "black-and-blue spots" in appearance and duration

Once the eruption is full blown, the malaise and other evidences of ill health which characterize the period of invasion clear up very quickly Sometimes between the morning and afternoon of the same day the patient will seem to become cured of the disease. The fever suddenly drops, the signs of catarrh rapidly clear up, the patient ceases feeling very miserable and the appetite quickly returns

The concomitant symptoms of the rash may be quite variable The tongue is often coated and with swollen

papillæ, especially along the margins; thus it is occasionally very similar to the strawberry-tongue of scarlet fever. The voice is often hoarse, and a mild cervical lymphadenitis is sufficiently common to be considered part of the disease. There may be a mild delirium. There often is a febrile albuminuria, and the diazo reaction is said usually to be positive, though negative in rubella.

IV. **Period of Convalescence With Desquamation.**

Desquamation.—Following the disappearance of the exanthem there is usually a fine branny desquamation, especially of the face and trunk, lasting two or three days. The hands and feet are ordinarily not involved.

In uncomplicated cases the temperature remains normal after its rapid fall and, with the exception of the pigmentation and the cough which are apt to last one or two weeks, the evidences of the disease clear up rapidly. After an attack of measles children usually regain their normal strength very quickly, but an adult is apt to feel fatigued for some days after the other evidences of the disease have disappeared.

Severe Cases.—Quite rarely at the present time, cases of apparently, overwhelming infection and intoxication occur, with rapid rise of temperature to around 105° F. and with marked cerebral disturbance shown by delirium, convulsions or stupor There is extensive involvement of the respiratory mucous membranes, cyanosis, rapid feeble pulse, and the early appearance of a massive, brownish-purple, confluent general eruption; or the eruption may be faint and the skin pale and "clammy," due to failing circulation. Death may occur as early as the second or third day of the disease Hemorrhages from all the mucous membranes of the body even to an uncontrollable degree have been reported.

Mild or Modified Cases.—These are observed in patients who have a partial immunity, such as infants whose inherited immunity has not entirely disappeared, and likewise other patients who have received a partially protective dose of a specific serum, such as the serum of convalescent patients. Features of these mild or so-called modified cases are as

PLATE VI



Showing a case of measles at the height of the disease, with the exanthem marked on the face and appearing on the body, also conjunctival congestion and mouth-breathing

(Schamberg and Kolmer, Acute Infectious Diseases)

follows: The incubation period is somewhat lengthened to between ten and twenty days. There is only a moderate rise of temperature, and this fever may last but two to four days. The period of onset or invasion is materially shortened, and the catarrh is much less severe than in the usual type of case, the conjunctivitis, coryza and cough being either mild or atypical in evolution. There is little malaise Koplik's spots and the enanthem may fail to appear, and the exanthem may hardly resemble that of ordinary measles being rather sparsely scattered over the face and body and to a less extent over the extremities The constitutional reaction is decidedly less marked than in average cases; complications are very rare; and owing to the diminution of the catarrh these modified cases are not very contagious. A diagnosis occasionally can be made only by means of the history of exposure and of receiving an injection of anti-measles serum.

Relapses or recurrences of the symptoms shortly after the first attack have been reported. Apparently well-authenticated second attacks have also been described, but in the vast majority of instances where patients state they have had measles more than once the diagnosis was incorrect in all but one of the so-called cases

THE COMPLICATIONS OF MEASLES

The complications of measles are usually those of a secondary infection superimposed on an already inflamed mucous membrane The most common secondarily infecting organism is a streptococcus Death in measles is almost always due to complications, bronchopneumonia being present in over 90 per cent of fatal cases

Some complication should be considered present whenever the fever fails to return to normal after the complete appearance of the exanthem, or whenever leukocytosis appears after the stage of invasion. Complications are relatively uncommon in private practice where patients are usually

isolated from all other sick people and can receive more satisfactory individual care In contagious disease hospitals and elsewhere secondary infections should be considered quite as contagious as the primary disease itself. The usual complications of measles are as follows in the order of frequency:

1. **Otitis Media.**—In hospitals without individual isolation nearly every case of measles may be complicated by a purulent otitis media, but by proper technic alone the incidence can be held down to 10 to 30 per cent, depending on the condition of the patients on admission. At the Willard Parker Hospital in the three years 1936–1938, 16 1 per cent (763) of 4,736 cases of measles were complicated by otitis media. The incidence of otitis in patients cared for in [illegible]

to remove almost entirely the likelihood of ear infections in measles

Otitis media is usually evidenced by a rise in temperature, by pain localized in or behind the ear, and by a red and bulging eardrum. However, particularly in infants, this complication frequently occurs without appreciably affecting the temperature curve, or even while the fever is returning to normal or is remaining normal, and it is not detected except by examination of the drums or by the discovery of a purulent discharge from the infant's ear Mastoiditis, formerly apt to follow about one-eighth of the cases of otitis media in measles, has been almost completely prevented by present-day methods of treating otitis with cleanliness and antibiotics.

2. **Bronchopneumonia**—Bronchopneumonia is present in nearly all fatal cases of measles and until recent years was present in about one-eighth of hospital cases. This high incidence in hospital patients was due to the fact that usually only the sickest measles patients are sent to hospitals In private practice bronchopneumonia is relatively uncommon in measles. Its presence is shown usually by the persistence

of the fever, by a marked increase in the pulse and respiratory rates, and by the prostration of the patient. The physical signs customarily found in a mild bronchitis may be considered normal to measles, but the additional presence of localized or widely distributed fine and coarse râles, as well as the physical signs of consolidation, may confirm the diagnosis of bronchopneumonia, a diagnosis which can often be presumed from the temperature chart alone

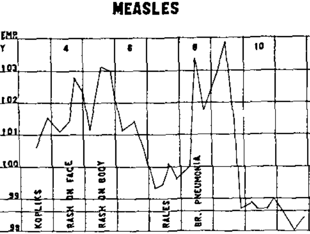


FIG. 32 —Showing an average case of measles in a boy, aged seven years, complicated during convalescence by a short attack of bronchopneumonia

By means of successive roentgenograms Kohn and Koiransky have demonstrated pneumonic infiltration in about three-fifths of hospital patients less than four years of age with measles and in about two-fifths of patients four years of age and over. Furthermore, in those patients who showed infiltration at any time, it was found before or during the height of the eruption in the majority, but it was usually more dense during the receding eruptive or posteruptive stages In many cases showing pulmonary infiltration radiologically, no definite physical pulmonary signs could be made out.

3 **Cervical Lymphadenitis.**—Cervical lymphadenitis to a sufficient degree to be considered a complication, is found in about 3 to 5 per cent of hospital cases. With the help of the sulfonamides or penicillin, this usually resolves without breaking down to abscess formation but occasionally an abscess does form and has to be incised.

4. **Laryngitis.**—Laryngitis commonly is merely catarrhal, and is shown by hoarseness or loss of voice, but it may be so severe as closely to resemble laryngeal diphtheria in its symptoms and course. A membrane, usually due to infection with a streptococcus and often a co-existing staphylococcus, may form in the larynx, and extreme respiratory obstruction may occur A severe laryngitis in measles is a very serious complication and the prognosis is especially poor if surgical treatment of the obstruction by tracheotomy or intubation seems necessary. About 1 per cent of hospital cases are apt to have enough laryngitis to produce symptoms of *respiratory obstruction.*

5 **Encephalitis**—Encephalitis (often more accurately an encephalo-myelitis) is a comparitively rare though important complication of measles, occurring in approximately 0 1 per cent of cases, but in some epidemics rather more frequently. The patients are practically all under thirteen years of age. There is no definite relationship between the severity of the measles and the occurrence of encephalitis except that this complication practically never occurs in measles modified by gamma globulin. From three to six days after the onset of the exanthem, or less commonly at any other time during the course of the illness, there is a rather sudden increase of fever with headache and of stiffness of the neck. Delirium and convulsions are present in about one-half of the cases. Tremor, choreiform or athetoid movements, and aphasias are common, and spastic paralysis may appear.

The spinal fluid is clear but under increased pressure, with *10 to 300 or more cells, mostly mononuclear in type,* and with normal to slightly increased amounts of sugar and globulin and no bacteria. The electroencephalogram reveals the

presence of slow waves of high amplitude which replace the normal pattern The blood shows a polymorphonuclear leukocytosis

There is no specific therapy. Approximately 15 per cent of patients with this type of encephalitis die, and roughly 20 per cent of those who survive have residual manifestations of varying degrees of severity. These sequelæ include loss of mental capacity, convulsive disorders, cranial nerve injury and hemiplegia

6 **Other Complications** —Other complications of measles are uncommon with the possible exception of a febrile albuminuria which is customarily found in patients with high fever Various types of nephritis may be present, though not nearly so commonly as in scarlet fever Sinusitis, purulent conjunctivitis, meningitis, or simple meningismus may occur. The usually fatal gangrenous infection of the mouth known as noma, or cancrum oris, is fortunately rarely met. There is an increased susceptibility to secondary infections with other contagious diseases, particularly diphtheria, erysipelas and whooping cough

A measles patient who at other times shows a positive skin test for tuberculosis may show only a negative test during a period of three to six weeks There is good authority for the statements that measles has little if any effect on well stabilized primary tuberculosis and that even active cases may or may not be aggravated However, in Greenland in 1951, the measles led to the outbreak of tuberculosis in many cases. Previously existing tuberculosis may make an attack of measles more serious The roentgen-ray appearance of the lungs in measles, because of the small scattered patches of peribronchial infiltration, may resemble and be mistaken for miliary tuberculosis

THE DIFFERENTIAL DIAGNOSIS OF MEASLES

1 *Rubella (German Measles)* —Here the eruption is quite variable, but it is usually pinker and may appear first on the

3. **Cervical Lymphadenitis.**—Cervical lymphadenitis to a sufficient degree to be considered a complication, is found in about 3 to 5 per cent of hospital cases. With the help of the sulfonamides or penicillin, this usually resolves without breaking down to abscess formation but occasionally an abscess does form and has to be incised.

4. **Laryngitis.**—Laryngitis commonly is merely catarrhal, *and is shown by hoarseness or loss of voice, but it may* be so severe as closely to resemble laryngeal diphtheria in its symptoms and course. A membrane, usually due to infection with a streptococcus and often a co-existing staphylococcus, may form in the larynx, and extreme respiratory obstruction may occur. A severe laryngitis in measles is a very serious complication and the prognosis is especially poor *if surgical treatment of the obstruction by tracheotomy* or intubation seems necessary. About 1 per cent of hospital cases are apt to have enough laryngitis to produce symptoms of respiratory obstruction.

5. **Encephalitis.**—Encephalitis (often more accurately an encephalo-myelitis) is a comparitively rare though important complication of measles, occurring in approximately 0.1 per cent of cases, but in some epidemics rather more frequently. The patients are practically all under thirteen years of age. There is no definite relationship between the severity of the measles and the occurrence of encephalitis except that this complication practically never occurs in measles modified by *gamma globulin. From three to six days after the* onset of the exanthem, or less commonly at any other time during the course of the illness, there is a rather sudden increase of fever with headache and of stiffness of the neck. Delirium and convulsions are present in about one-half of the cases. Tremor, *choreiform or athetoid movements, and aphasias* are common, and spastic paralysis may appear.

The spinal fluid is clear but under increased pressure, with 10 to 300 or more cells, mostly mononuclear in type, and with normal to slightly increased amounts of sugar and globulin and no bacteria. The *electroencephalogram reveals the*

in scarlet fever than in measles. Leukocytosis is present in scarlet fever but not in uncomplicated measles

3. *Serum Rash.*—This is usually composed of two elements, erythema and urticaria, with one or the other predominating and the latter accompanied by much itching There is fever for several days, also edema of the skin, especially of the face, and occasionally joint pains. At times, however, cases are found where the eruption is quite definitely morbilliform. There is a history of a recent administration of a foreign serum

4. *Drug Rashes.*—Drug rashes may resemble the eruption of measles, particularly if due to antipyrin, acetanilid, phenacetin, quinine, copaiba, the sulfonamide group of chemicals, and occasionally belladonna

5. *Roseola Infantum (Exanthem Subitum)* (also see page 255).—This is a clinical entity characterized by three or four days of fever ranging from 102° to 103° F. or more, without apparent cause or accompanying prostration, after the fever falls a usually mild punctate or macular reddish-pink eruption appears which is distributed generally on the body, less on the face and extremities, and which lasts only one or two days. The eruption is often indistinguishable from that of rubella except that it is relatively slight on the cheeks and nose. A moderate leukopenia with a considerable relative increase in the lymphocytes develops during the fever and clears up as the eruption disappears There are no Koplik s spots Except for the preliminary fever and the blood count, this disease may be closely similar to modified measles In the great majority of cases it is found in children in their second or third years It is fairly certainly due to a virus which is present in the blood stream at least the first day of the fever The incubation period seems to be eight or ten days It is apparently only slightly contagious, second cases in a household rarely occurring, but institutional epidemics in orphan asylums have been reported. Isolation is ordinarily not necessary

body rather than on the head. The first day the rash is apt to look like measles and the second day like scarlet fever, while the third day it usually is practically gone. It is not followed by staining or pigmentation of the skin. The fever, if any, does not commonly go above 101° F. and lasts only about two days There is slight if any catarrh, and *constitutional symptoms are mild during the presence of the rash* and often absent in the prodromal period. The suboccipital, or posterior cervical lymph nodes are characteristically swollen and tender, but some swelling of any of these lymph nodes can also occasionally be found in measles. Convalescence is rapid and complications are rare Owing to its variability and occasional resemblance to more serious diseases, rubella should be diagnosed cautiously, particularly in the absence of an epidemic.

2. *Scarlet Fever*.—Practically no prodromal period is found, the onset being sudden and the fever usually maximum within the first forty-eight hours. The eruption is characteristically erythematous and punctate rather than macular, and does not usually appear above the chin-ear line. On the arms and legs, however, the eruption of scarlet fever is not infrequently blotchy and suggestive of measles. The noteworthy strawberry-tongue of scarlet fever is occasionally closely simulated in measles. Coryza in scarlet fever usually denotes a secondary infection, but is characteristic of measles. Both diseases desquamate on the face and body, though to a different degree, but measles usually does not desquamate on the hands nor as markedly on the feet as does scarlet fever. Brownish stains on the body during convalescence are indicative of measles rather than scarlet fever

Characteristic features of measles and scarlet fever differ, such as Koplik's spots in measles as opposed to angina, circumoral pallor, and Pastia's sign in scarlet fever. The liability to certain complications also differs. Pneumonia occurs frequently in measles, but quite uncommonly in scarlet fever. Nephritis and arthritis are far more common

THE MORTALITY AND PROGNOSIS OF MEASLES

The older the child the better is the prognosis. The second half of the first year the mortality is usually highest, having been over 25 per cent in some hospital series in the years before the sulfa drugs became available, but around 8 per cent in general populations. In New York City over a considerable period of years the average death-rate was 2 to 3 per cent, the percentage varying with individual epidemics and with the concurrence of streptococcic, pneumococcic, and similar infections, but in recent years the mortality has been less than 0.2 per cent. In the past, in hospitals for contagious diseases the mortality has run between 8 and 20 per cent, and around 1890 in Paris hospitals it was 33 to 48 per cent, but where patients are all individually isolated, thereby minimizing the spread of secondary infections, and where antibiotics are available, even hospital mortality in measles may be kept as low as 0.2 per cent. From 1943 to 1952 at the Willard Parker Hospital there were only 14 deaths in the 8,863 measles cases treated. The outcome of the illness may depend on the child's previous condition and resistance, the virulence of the infection, and the presence of complications, and in particular on the nursing and medical care. Before the days of penicillin, deaths were almost always due to a terminal bronchopneumonia or some other secondary infection, but in recent years such deaths as have resulted from measles have almost all been caused by encephalitis.

PERIOD OF INFECTIVITY

Inasmuch as the infective virus is present in the secretions from the nose and throat, the period of greatest infectivity is when these secretions are most marked, that is, during the period of invasion. As a rule the measles patient may be considered actively contagious from the onset of his catarrh (that is, at least three days before the appearance of the rash) until such time as the catarrh has ceased, which is usually

6 *Syphilis.*—The macular rash of syphilis must be considered when an adult is thought to have measles, particularly if there is no catarrh and no fever.

7. *Smallpox.*—The great Arabian Rhazes, a thousand years ago in his classic account of smallpox, confused it with measles, and today, when smallpox exists in a community, this differentiation must be borne in mind. The hyperpigmented confluent eruption of severe smallpox may be closely similar to the hyperpigmented eruption of measles, and each of these two diseases is preceded by a prodromal stage of almost the same duration Marked backache and severe constitutional symptoms are more typical of smallpox, and the characteristic lesion of smallpox is the pock.

8 *Coryza* —Simple head colds, particularly when recent in origin and increasing in severity, must always be differentiated from the prodromal stage of measles. The abnormal eye signs of measles involving the caruncle and plica semilunaris (see page 217) are very useful in the differential diagnosis, and when marked are almost pathognomonic. These two diseases, however, may be indistinguishable until the enanthem and Koplik's spots do or do not appear, as the case may be.

Koplik's spots also must be differentiated from various other conditions.

1. *Food particles*, such as milk or bread crumbs

2. *Sprue* or *thrush*, where the whitish specks and plaques are found not only on the cheeks but on the gums, tongue, and palate.

3. *Aphthous stomatitis*, in which small red spots are scattered in the mouth, each spot being surmounted with a yellowish or pale yellow vesicle either intact or ruptured The intervening mucous membrane of the mouth is normal, the eruption being discrete and never confluent.

4. *Normal epithelial pearls*, which are elevated yellowish-white specks of varying size and shape situated under the mucous membrane of the cheeks and shining through. There is no red halo.

school. If given what is intended to be a mitigating or modifying dose, the child may continue in school but between the eighth and fifteenth days after exposure should be kept home if there is any evidence of ill health. If given no protective serum, the exposed susceptible child should be kept out of school from the eighth day after the first exposure until the thirteenth day after the last exposure

On readmission to school the exposed child should have a normal temperature and be free from all evidences of catarrh.

In New York City susceptible contacts are allowed to continue in school because there are grave doubts that rigid quarantine regulations accomplish anything except much loss of schooling, but careful supervision is urged However, particularly in a nursery-school, a child exposed at home should certainly not be allowed to expose a so-called "clean" or non-exposed group.

When in a hospital ward a case of measles develops and has been removed, protective doses of gamma globulin should be given to the exposed children who have not had measles, and then during the next three weeks only those new cases should be admitted who have had measles or have received gamma globulin

PROPHYLAXIS IN MEASLES

With measles, as with chickenpox, over 85 per cent of susceptible children exposed at home will develop the disease, and 20 per cent or more of those exposed at school

Children exposed to measles can by the injection of variable amounts of several different human blood products such as parental serum, convalescent serum, but particularly gamma globulin, receive either a short but complete protection, or a partial protection By the latter an incubating measles infection can be modified often to a trivial illness.

If during the first five or six days after exposure an individual is inoculated with a sufficient dose of gamma globulin, *complete protection* may be obtained for possibly four weeks,

soon after the return of the temperature to normal. After the fifth day from the appearance of the eruption the patient may be considered no longer contagious. The disease is apparently not spread after this period even though there be secondary infections.

TABLE 6.—THE RESULTS OF CLASSROOM EXPOSURE TO MEASLES.

Children in class	Days before the rash appeared		Susceptible children exposed		Caught measles	
5 children in class	1 day before the rash appeared	exposed	24 susceptible children,	of whom	5 caught measles, or	20.8%
10 "	2 days "	"	56	"	11 " "	24.4%
18 "	3 "	"	122	"	19 " "	18.4%
5 "	4 " "	"	26	"	0 " "	0.0%
6 "	5 " "	"	38	"	0 " "	0.0%

Showing that the last three days before the rash appears, children who continue in school are dangerous to their classmates. During the fourth and fifth days before the appearance of the eruption, however, there ordinarily is no danger. (Courtesy of the Arch. Pediat.)

ISOLATION AND QUARANTINE IN MEASLES

Isolation varies in length according to local regulations. In New York City isolation is ended five days after the appearance of the exanthem. Cases of modified measles may be released from isolation the second day after the disappearance of all evidences of the disease.

Exposed Persons.—A child is considered exposed if he has been in direct or indirect contact with the patient at any time during the disease, including the three days preceding and the five following the appearance of the rash, and particularly until the catarrh has ceased. Contact with the patient need not be direct, but may be indirect through a third person who has come directly from the patient, such as a ward nurse, a house-maid, or a mother. A child must be considered susceptible unless he has had measles or has within four weeks received an immunizing injection of gamma globulin.

Quarantine regulations will depend on what is done for the exposed susceptible child. If given a completely protecting dose of gamma globulin, the child may continue in

virus. Pooling sera from many donors naturally increases this danger greatly. The virus of this disease is not carried by gamma globulin, so this is the safest and most practical preparation to use. However, it is not always available

Gamma Globulin (Human Immune Serum Globulin) —This is a concentrated solution of the antibody-bearing globulin fraction derived from pooled normal human blood plasma. Each ml contains the antibody equivalent of 25 ml of original plasma obtained from many adult donors. The majority of these donors have had measles at some time and retain the specific antibodies Because of its concentration, gamma globulin is the most potent prophylactic yet developed against measles. It cannot cause jaundice

For prevention of measles, the dosage is based on 0 1 ml per pound of body weight but in general 2 0 to 2 5 ml. is recommended for children under six years of age and 5 to 7 ml for those over, the injection being given intramuscularly preferably in the buttocks, and during the first four days after exposure

For modification, a fourth as much is given, or 0 02 to 0 025 ml per pound of body weight, preferably in the interval from four to seven days after exposure

The dosage of the preparation must vary according to a number of factors The time that has elapsed since the child was exposed, and his age and size are of prime importance The heavy and repeated infections of home exposures require larger doses than do the probably lighter infections of classroom, hospital ward, and especially outdoor exposures Increased doses are particularly necessary when the exposed child is already suffering from scarlet fever or diphtheria, also children one to four years old seem to require relatively more than those a little older Hence, it is not practical to specify dosages for the many combinations of circumstances that are possible For children four to six years old, in most instances, 1 0 ml of gamma globulin given six or seven days after the first exposure produces a satisfactory degree of modification.

and the attack of measles due to such exposure may be entirely prevented, but later than the sixth day complete protection cannot be assured. In this connection it must be remembered that exposure in a family dates back to at least three days before the first evidence of the exanthem in the patient.

Complete protection is desirable for babies still in the first two years of life, for patients in hospital wards, and for children suffering with tuberculosis and other cachectic diseases or infections

For other children, especially those apparently in good health, it is usually wiser to give smaller doses of the serum so as to provide only *partial protection or modification* A child may then develop a mild or modified case of measles, but he thereby almost always acquires protection against measles for life, whereas the complete temporary protection derived from the larger doses of serum is usually entirely gone after three or four weeks, leaving the child as susceptible as before the injection. Some authorities believe that even if given as late as the first day of fever, that is, just before the onset of definite symptoms, a large dose of gamma globulin will modify the oncoming measles.

It is not yet known how much of a case of measles a child must have to secure permanent protection, but it is probably essential that fever, catarrh, and an exanthem be definitely present though in a mild form.

It is well to add that *every* susceptible person of any age who is known to have been heavily exposed to measles should be given the benefit of a modifying dose of gamma globulin or its equivalent Even adults occasionally die of measles Modification of an oncoming measles is everybody's right.

The only known source for protective measles antibodies is human blood The antibodies can be given in the forms of convalescent serum, parental serum and whole blood, gamma globulin, and placental extract. Of these, convalescent serum and parental serum have been in use the longest, but there is the danger of the patient's being given a hepatitis

virus. Pooling sera from many donors naturally increases this danger greatly. The virus of this disease is not carried by gamma globulin, so this is the safest and most practical preparation to use. However, it is not always available.

Gamma Globulin (Human Immune Serum Globulin).—This is a concentrated solution of the antibody-bearing globulin fraction derived from pooled normal human blood plasma Each ml contains the antibody equivalent of 25 ml of original plasma obtained from many adult donors The majority of these donors have had measles at some time and retain the specific antibodies. Because of its concentration, gamma globulin is the most potent prophylactic yet developed against measles. It cannot cause jaundice

For prevention of measles, the dosage is based on 0.1 ml per pound of body weight but in general 2 0 to 2 5 ml is recommended for children under six years of age and 5 to 7 ml for those over, the injection being given intramuscularly preferably in the buttocks, and during the first four days after exposure.

For modification, a fourth as much is given, or 0 02 to 0 025 ml per pound of body weight, preferably in the interval from four to seven days after exposure

The dosage of the preparation must vary according to a number of factors The time that has elapsed since the child was exposed, and his age and size are of prime importance. The heavy and repeated infections of home exposures require larger doses than do the probably lighter infections of classroom, hospital ward, and especially outdoor exposures Increased doses are particularly necessary when the exposed child is already suffering from scarlet fever or diphtheria, also children one to four years old seem to require relatively more than those a little older Hence, it is not practical to specify dosages for the many combinations of circumstances that are possible. For children four to six years old, in most instances, 1 0 ml of gamma globulin given six or seven days after the first exposure produces a satisfactory degree of modification

Gamma globulin must not be administered intravenously because in addition to the desired antibodies it also contains a concentration of the depressor substance present in normal plasma. Therefore, after puncturing the muscle and before making the actual injection, due care should be observed to withdraw the piston of the syringe slightly and watch for blood entering the barrel, to insure that the injection is not intravenous. If allowed to stand even a few minutes in a syringe, this preparation will cause the piston to stick or "freeze." Furthermore, this globulin preparation is thick and requires a 22- or 23-gauge needle for easy filling and injection. Reactions following the intramuscular injection of this product are rare. When gamma globulin is not available, 5 to 10 ml. of convalescent serum, or 15 to 30 ml. of parental serum, injected deep in the buttocks of an exposed child within six days of the exposure will mitigate the case of measles in the great majority of cases.

For *active immunization* Rake and Stokes and their co-workers prepared a measles vaccine by attenuating the virus by growing it for successive generations on chick embryo tissue. Using this vaccine they inoculated several hundred children producing in them an essentially harmless form of modified measles which, however, apparently failed to protect the majority of the children from subsequent infection resulting from normal exposure to the disease. Although it appears that active immunization against measles appears to be possible, no vaccine against measles is available commercially.

THE TREATMENT OF MEASLES

This logically falls under five headings: specific treatment, the comfort of the patient and general management, the isolation of the patient with the prevention of the spread of the infection to other people, the prevention of secondary infections, and the treatment of complications as they arise.

Specific Treatment.—It has been found that in 80 per cent of cases so treated, 50 ml. of convalescent serum given

intravenously (or 15 to 30 ml. of gamma globulin given intramuscularly) in the preëruptive stage at least one day before the appearance of the rash, will modify an oncoming measles This may prove of considerable value where measles is developing as a complication of some other exhausting disease, and is the only known instance, in man, where a serum apparently has therapeutic value in a virus disease. Generally, this course is not necessary and no attempt to modify the disease at this stage should be attempted

Comfort of the Patient and General Management —The patient should be in bed *from the onset of the fever until three* days after the return of normal temperature Fluids should be forced throughout the illness The air should be fresh but the temperature of the room should be kept at 70° F or above, and the patient should be comfortably warm, but not hot The diet during fever should be largely of fluids and carbohydrates, such as orange juice, buttermilk, broth thickened with rice or barley, beef tea, cooked cereal, toast, zwieback, junket, and apple sauce. As a rule, children with a fever do better without meat, eggs, or fat Sweet milk is occasionally poorly tolerated during fever, particularly unless the cream has been removed or some milk sugar added After the temperature has returned to normal, cooked vegetables, cooked fruits, and simple desserts are next

valueless Codeine, paregoric, brown mixture, or Dover's powder in small doses may prove helpful. The bed should be turned so that its head is toward the light, or the eyes may be protected from bright light by wet compresses or colored glasses, but the shades need not be drawn, as is customary Borated petrolatum may be applied to the lid margins to prevent sticking The coryza should be combated by suitable nosedrops, and camphor-ice rubbed on the nostrils is usually comforting When the headache and malaise are marked and the cough not sufficient to warrant codeine,

aspirin is helpful in small repeated doses or in combination with phenacetin and caffeine. Wrapping the patient in blankets helps occasionally to bring out the exanthem. Itching may be quite troublesome and may be relieved by bromides or by the application of calamine and zinc lotion or by starch baths Temperatures of 104° F. or over may be treated by cooling sponges, by aspirin, or by an icebag on the head, but alcohol is often disturbing on an exanthematous skin In general, cleanliness, rest, warmth, light, fresh *warm* air, good food, and good nursing are essential

Isolation and the Prevention of Spread of the Disease.—The infection may be carried by cough droplets at least 5 feet, possibly further, hence everything within 6 feet of the patient's bed should be considered contaminated and infectious whether the patient has touched it or not. All the details of medical aseptic technic should be very strictly carried out, especially where susceptible children are living in the same building, as in a hospital ward or a home A third person can very readily carry the measles infection directly from one end of a ward to a patient at the other end of the ward or elsewhere under the same roof. Ultra-violet ray barriers are effective in limiting the spread of the disease in wards In fresh air, the measles virus dies quickly and it is practically impossible to carry the disease through the open air for any appreciable distance However, a doctor going from a measles patient to some other child in the same home or immediate vicinity should exercise every precaution of aseptic technic, or better, he should go to the other child first

Prevention of Secondary Infections.—Inasmuch as secondary infections are apparently nearly as contagious as is the primary measles, every measles patient should be isolated from every other measles patient, particularly from those already ill with a secondary infection. Everyone, doctor, nurse, or attendant, should wash the hands carefully before touching a patient to prevent carrying secondary infections to him Everyone suffering from such infections as a head cold should keep away from the measles patient entirely. Cleanliness of

the patient is also essential, including the mucous membranes of the eyes, nose, and mouth. A daily cleansing bath should be given. The eyes should be washed frequently with a solution of boric acid. The mouth should be rinsed occasionally with a solution of milk of magnesia or of liquor antisepticus, U.S.P., or of alkaline antiseptic solution, U.S.P. The patient should particularly be protected against chilling.

There is evidence that the routine administration of sulfadiazine or of an antibiotic in moderate dosage during the height of the disease is of value in markedly reducing the incidence of complications, especially of those such as otitis media which are usually caused by hemolytic streptococci and pneumococci. (For dosage and precautions, see Chapter 3, p. 56.)

Treatment of Complications.—Otitis media occurring in measles is in the great majority of cases due to a streptococcus, and is quite certain to be accompanied by the formation of pus in the middle ear, unless early and positive measures are instituted to combat the infection. The administration of the antibiotics (see page 65) is indicated in adequate dosage. The instillation in the canal of warmed drops of a hygroscopic glycerine serves to relieve the congestion and the pain and it is also wise to use nose sprays or inhalations that might shrink the mucous membrane of the opening of the eustachian tube to the affected ear. If after twelve to twenty-four hours, a bulging opaque drum suggests the presence of pus in the middle-ear a myringotomy is of course indicated, but in most instances, with the treatment described, conditions warranting this operation can be prevented. Discharging ears should be kept scrupulously clean by means of sterile swabs and, when the discharge is thick, by occasional gentle irrigations with warm boric acid solution. The possibility of involvement of the mastoid bone should receive constant consideration.

Hemolytic streptococci are present in nearly every case of measles pneumonia, but pneumonococci can also be isolated from the sputum or the nasopharynx of many cases. The

antibiotics are indicated and are remarkably curative even of the pneumonias due to mixed infections, the temperature usually becoming normal in twenty-four to thirty-six hours from the start of adequate medication, although the lung consolidation and roentgen-ray shadows may persist the usual length of time.

Thus most cases of pneumonia complicating measles respond well to these remedies which, however, prove ineffective on a small proportion of cases, those which are presumably caused by a virus, either that of measles or some other For these cases no specific therapy is available and supportive treatment is indicated with the free use of oxygen

Cervical lymphadenitis is combated by antibiotics and such cold applications as an ice-collar or cold wet compresses, also by vigilance in the cleanliness of the nose and throat, which are the usual sources of supply of the lymph-node infection When abscess formation of the lymph nodes seems inevitable or already present, hot compresses serve to localize the infection, and are advantageous before and after the abscess is opened and drained.

The laryngitis of measles in its milder forms is primarily due to the measles virus itself which causes inflammation of all the upper respiratory mucous membranes, but in the more severe forms it is usually due to a streptococcus, although the possibility of a diphtheritic infection should not be overlooked Direct inspection of the vocal cords with culture and aspiration of mucus is indicated and if a diphtheritic membrane is found, large doses of antitoxin should be given at once. Subsequent steam inhalations are usually helpful but in an occasional case the administration of oxygen is much more beneficial Of medicines, in addition to the ever useful antibiotics, small doses of ipecac may be helpful

For measles encephalomyelitis there is no specific remedy. Convalescent serum in very large doses and cortisone have been employed, but there is no convincing evidence that they are of value. Treatment is entirely symptomatic. Convulsions are treated by subcutaneous injection of sodium

phenobarbital, by rectal instillation of paraldehyde or avertin (tribromethanol) or by inhalation of chloroform

When the medulla and pons are involved problems similar to those which occur in bulbar poliomyelitis are encountered These include difficulty in swallowing and shallow, irregular respirations A child who is unable to swallow is in great danger of asphyxia from aspiration of saliva and mucus into the trachea and bronchi Efforts should be made to prevent such an occurrence by elevating the foot of the bed and by constant aspiration of the mouth and pharynx When these measures are not effective, a tracheotomy should be performed to provide an unobstructed airway and to facilitate removal of material which has been aspirated into the trachea. Irregularities of breathing due to involvement of the respiratory centers require treatment with the tank respirator or the electrophrenic respirator

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8

Rubella

Synonyms.—German measles, Rose measles; Rotheln, and many other terms. Any name for rubella that includes the name "measles" is undesirable, because of the tendency of the uninformed to confuse this disease with measles. Rubella is a disease distinct from all other diseases, and imparts to its victims immunity against itself alone.

History—According to Wesselhoeft, rubella was first described by two German physicians, de Berger in 1752, and Orlow in 1758 The disease eventually became known as roetheln or Rotheln, and later as German measles because of the interest of German writers in this disease In 1866 Henry Veale introduced the term "rubella."

Definition—An acute specific contagious disease characterized by slight constitutional manifestations and upper respiratory catarrh, by swelling and tenderness of posterior cervical lymph nodes, and especially by an eruption consisting of diffusely distributed rose-colored macules. This eruption may suggest measles the first day, scarlet fever the second day, and be gone the third day

Descriptions of this disease vary greatly. It is highly probable that because of the lack of specific features for diagnosis, a number of different conditions have been considered to be rubella and have been described as such. So also, the cases that have been reported with severe complications and even fatal outcome, may very likely have been incorrectly diagnosed, and what was primarily scarlet fever, true measles, or any one of a number of other conditions may have been mistaken for and described as rubella Rubella

is a very mild disease and unless it occurs early in pregnancy is almost always unaccompanied by complications or sequelæ of any moment.

THE ETIOLOGY OF RUBELLA

Exciting Cause.—The exciting cause of rubella is a filterable virus which is present in the secretions of the nose and throat and in the blood stream in the early eruptive stage. Hiro and Tasaka demonstrated that filtered nasal washings injected into susceptible children caused a characteristic eruption, and later Habel obtained similar results in monkeys. Krugman, Ward and their associates in this country have transmitted the disease in series to human volunteers.

Season and Age.—The disease occurs more commonly in the late winter and spring. In the four months of March to June 1935, there was a very extensive epidemic in New York City, 22,275 cases being reported. Another and similar epidemic occurred in the spring of 1942. More recently Krugman and Ward have reported a striking seasonal concentration of rubella during the spring months in New York City.

The disease is ordinarily not quite so contagious as are measles and chickenpox. The average age is rather higher than for measles, because of the lesser likelihood of a patient's contracting the disease at the first exposure. For instance, many more college students are seen with rubella than with measles, presumably because most students have had measles before they reach college. After forty the disease is rarely met, and infants under the age of six months are probably immune if their mothers are immune. It is also probable that many of the cases in young children reported as rubella are incorrectly diagnosed.

Rubella is apt to occur in epidemics, and since it breeds true, *i. e.*, can cause only rubella in other people, the diagnosis in epidemics is made simpler. In March, 1918, there were admitted at one time to the British Contagious Disease

Hospital at Rouen, 67 young recruits from a battalion that had been landed at Le Havre the day before, having been rushed over to help stem the German offensive. Of the 67 soldiers taken off the train, one was found to have Koplik's spots and went on to have a normal case of measles, but the other 66 were all diagnosed as rubella, and as such were isolated together Fortunately, no subsequent cross-infections developed from this train exposure to measles. Of the 66, only 2 were sick enough to be willing to stay in bed

Authentic sporadic cases are not common, and except in the presence of an epidemic, rubella should be diagnosed with caution.

THE PATHOLOGY OF RUBELLA

There are no known pathological lesions that are characteristic of rubella

With the appearance of the eruption the blood shows a moderate leukopenia with reduction particularly of the polynuclear forms. The lymphocytes and monocytes increase in number during the next day or two and the total count is again normal in a week or ten days

Pregnancy and Rubella.—In 1941, Gregg of Australia first called attention to the frequency with which congenital cataracts followed the occurrence of rubella in the early months of the mother's pregnancy Since that time numerous reports have made it clear that rubella in the mother may result in the "rubella syndrome" in the newborn infant, provided that the infection occurs during the first trimester of the period of gestation. The syndrome includes congenital cataracts, deafness, microcephaly, mental retardation, defects of the septa of the heart, and persisting patency of the ductus arteriosus. These malformations may be found singly or in various combinations. Spontaneous abortion and stillbirth also appear to be caused by rubella A possible explanation of the deformities is that the lens of the eye and the interventricular septum of the heart are developed during the second month of fetal life and embryonic tissue is known

to be especially susceptible to virus infections In the six-week embryo the blood supply begins to reach the lens but does not yet supply the retina. Hence, rubella virus can reach the lens only, and the eye lesions caused by rubella are chiefly in the lens. Apparently the rubella virus is the only one that has been clearly proven to cause congenital defects

The risk of stillbirths and congenital malformations resulting from maternal rubella infection during the first trimester of pregnancy has been variously estimated from 10 to 90 per cent. The higher figure has been arrived at from retrospective studies, and is therefore certainly too high. The lower figure represents an average of several prospective studies, made by selecting the cases to be studied before the birth of the child An average of such studies indicates 15 to 20 per cent of infants of mothers who have experienced rubella infection in the first trimester will be stillborn or will have congenital anomalies, as compared with 3 to 5 per cent of controls

THE INCUBATION PERIOD OF RUBELLA

The incubation period is given variously from five to twenty-one days. Its duration is somewhat variable from epidemic to epidemic, but most cases of rubella may be found to develop early in the third week after exposure, with an average outside range of twelve to twenty-one days. When infected blood is given intramuscularly to volunteers, the incubation period of rubella is eleven to twelve days

THE CLINICAL MANIFESTATIONS OF RUBELLA

Symptoms.—During the incubation period there are no evidences of ill health, and there are usually no prodromal symptoms The period of invasion may last twelve to twenty-four hours, during which time there may be slight malaise, a slight head cold, a slight sore throat, even a little headache, and possibly fever to the extent of 100° F. or

thereabouts In the epidemic in New York City in 1935 and again in 1942, swelling and slight tenderness of the posterior cervical lymph nodes occasionally were present before the rash appeared, sometimes only a day or two in advance, but in isolated instances even four or five days. Experience with cases seen in 1955 has been similar. It is unusual for these early manifestations to be severe enough to make the patient willing to stay in bed. In fact, constitutional symptoms may be absent entirely. The majority of the 250 children observed by Krugman and Ward presented the simple syndrome of normal temperature or low grade fever, a three-day rash, and posterior-auricular and suboccipital lymphadenopathy The disease in adults is generally more severe, and arthralgia is occasionally found.

The exanthem is usually the first evidence of ill health to be noticed by the patient or the patient's associates. It is apt to appear first on the face and neck and spreads rapidly over the entire body in two or three hours' time, affecting the head, arms, and trunk, and the legs to a less extent The rash is characterized by innumerable small, discrete, pinkish spots or macules, which are slightly if at all elevated above the surface of the skin. The color is usually much lighter than is that of the eruption of measles, and is characteristically pink in contrast to the brownish-red of measles. The fine macules of rubella, even though very numerous, do not tend to form the blotchy, confluent patches of irregular outline that are found in measles, but rather tend to blend as they grow older to form a diffuse erythematous eruption, not unlike an old eruption of scarlet fever, except that the area around the mouth is usually extensively involved in contrast to the circumoral pallor of scarlet fever. The eruption of rubella fades readily on pressure The average [illegible] eruption may [illegible] rs, or it may [illegible] is it spreads, and the face and shoulders may be fairly clear when it is still marked elsewhere on the body. The most notable feature

about the eruption is its change in appearance in a few hours' time. As has been said, it may somewhat resemble measles the first day, scarlet fever the second day, and be gone the third day. A slight, fine desquamation may be observed after the more marked eruptions No pigmentation is found to follow this eruption, in contrast to measles.

Besides the eruption, the other notable feature of rubella is the involvement of the lymph nodes in the back of the neck. The nodes usually involved are the suboccipital glands found on each side of the external occipital protuberance, but in many cases the postauricular and submastoid glands may be found to be involved instead. Swelling and tenderness of these lymph nodes, particularly of the suboccipital group, are found in the great majority of the cases, and may be sufficient to cause the patient to hold the head rather stiffly on the neck. There also may be slight involvement of various other lymph nodes situated throughout the body, particularly the axillary and inguinal groups This glandular involvement ordinarily lasts from two to seven days, usually subsiding quickly after the rash has disappeared but its onset may precede the appearance of the rash by one to five days or it may survive after the rash for several days

Together with the eruption and the lymphadenitis there may be a mild congestion of the fauces, and it is usual to find a number of very fine red spots on the soft palate, sometimes called "Forchheimer's spots," but they are of no diagnostic significance Pain on swallowing is slight, less than one might expect from the appearance of the pharynx The mucous membrane lining the inside of the cheeks remains normal The orbital conjunctiva may become slightly congested, but there is no photophobia or anything suggesting

cases there may be as much fever as 101° or 102° F for two or three days, but when more than this is the case, particu-

larly in the absence of an epidemic, the diagnosis should be questioned.

Types.—Various types of this disease have been reported, such as a morbilliform type, a scarlatiniform type, and a severe type with catarrhal manifestations. Some cases have eruptions which throughout their course are suggestive of measles, and other cases at all times more closely suggest the eruption of scarlet fever. In view of the difficulty of diagnosis without any specific features such as serological tests or pathognomonic signs, it is difficult to say whether all the varieties described should be considered cases of rubella

TABLE 7.—CLINICAL ASPECTS OF EXPERIMENTAL RUBELLA

Subject	*Maximum Temperature, F*	*Rash**	*Lymph Node Enlargement**	*Leukopenia**
C. R.	100.4	+	++	0
J. G.	101.6	0	+	0
P. K.	100.8	0	++	++
N. K.	99.6	++	+	++
E. T.	101.6	+++	+++	0
K. L.	100.4	++	+	+
J. S.	99.0	++	+	0
S. E.	99.4	++	0	0
G. O.	99.8	++	++	0
C. N.	99.4	+++	+++	—
P. A.	99.6	+++	++	—
T. B.	99.2	+	+	—
M. I.	99.4	++	+++	—

* +++ = marked, ++ = moderate, + = minimal, 0 = none, — = not done (From Krugman and Ward, J. Pediat., *44*, 491, 1954.)

In the presence of an epidemic involving a considerable number of patients under close observation, such as in an institution, it is sometimes possible to recognize variations from the average case, at the same time noting the absence of any other disease. Rubella causes only rubella, but except under such well-controlled circumstances as the above, a disease that is found to vary to any extent from the typical picture, cannot safely be diagnosed as rubella.

Human infection with the virus of rubella can occur without the development of an eruption, but the diagnosis of such an infection can be made only under experimental circumstances[1] The variability of the natural disease has also been present in experimentally produced rubella This is shown in the accompanying table, which outlines the clinical manifestations in 13 volunteers in whom experimental rubella was induced. Two patients did not develop a rash, and 1 exhibited no lymph node enlargement Leukopenia was present in only 3 of 9 cases studied

THE COMPLICATIONS OF RUBELLA

Complications have been described in the medical literature, but they occur very rarely

A few cases of encephalitis were noted closely following attacks of rubella in both the 1935 and 1942 epidemics of this disease, the incidence being estimated at about one such case to 6000 cases of rubella. They were somewhat variable in their manifestations, but in general were similar to the encephalitis that complicates other virus diseases and with a similar mortality of 10 to 20 per cent. In the epidemics, such other so-called complications as were observed were probably merely coincidental occurrences.

THE DIFFERENTIAL DIAGNOSIS OF RUBELLA

In the matter of uncertainties and mistakes in diagnosis, rubella assumes considerable importance Scarlet fever and measles are usually, though by no means invariably, diagnosed correctly Rubella is frequently, if not usually, thought to be something else and various other conditions are often called rubella In general, rubella occurs in epidemics and in older children rather than infants Its changeable exanthem is distinctively intense on the face as well as elsewhere and there is a post-cervical lymphadenitis.

[1] Krugman *et al* J A M A, *151*, 285, 1953

larly in the absence of an epidemic, the diagnosis should be questioned.

Types.—Various types of this disease have been reported, such as a morbilliform type, a scarlatiniform type, and a severe type with catarrhal manifestations. Some cases have eruptions which throughout their course are suggestive of measles, and other cases at all times more closely suggest the eruption of scarlet fever. In view of the difficulty of diagnosis without any specific features such as serological tests or pathognomonic signs, it is difficult to say whether all the varieties described should be considered cases of rubella.

TABLE 7.—CLINICAL ASPECTS OF EXPERIMENTAL RUBELLA

Subject	*Maximum Temperature, F*	*Rash**	*Lymph Node Enlargement**	*Leukopenia**
C R	100 4	+	++	0
J G	101 6	0	+	0
P K	100 8	0	++	++
N K	99 6	++	+	++
E T	101 6	+++	+++	0
K L	100 4	++	+	+
J S	99 0	++	+	0
S E	99 4	++	0	0
G O	99 8	++	++	0
C N	99 4	+++	+++	—
P A	99 6	+++	++	—
T B	99 2	+	+	—
M I	99 4	++	+++	—

* +++ = marked, ++ = moderate, + = minimal, 0 = none, — = not done (From Krugman and Ward, J Pediat, *44*, 491, 1954)

In the presence of an epidemic involving a considerable number of patients under close observation, such as in an institution, it is sometimes possible to recognize variations from the average case, at the same time noting the absence of any other disease Rubella causes only rubella, but except under such well-controlled circumstances as the above, a disease that is found to vary to any extent from the typical picture, cannot safely be diagnosed as rubella.

fever maintains its punctate erythematous character throughout, and usually lasts from four to seven days The area around the mouth is notably pale and uninvolved by the eruption, and desquamation is usually a notable feature of the convalescence. Leukocytosis is found in scarlet fever, but in rubella there is ordinarily a slight granulocytic leukopenia The presence or absence of exposure to one or the other disease gives helpful information in the differential diagnosis, as does also a history of a previous attack of either scarlet fever or rubella The Schultz-Charlton blanching test is positive in scarlet fever

3 *Erythema Infectiosa* (so-called Fifth Disease) may sometimes be confused with mild Rubella. This is a disease which appears in small epidemics It is characterized by red "slapped-looking" cheeks and perioral pallor This precedes the appearance of a generalized evanescent rosy pink, blotchy, morbilliform eruption which is most marked on the upper extremities and buttocks As the rash fades a lattice-like appearance is noted, and itching may become very marked There is usually no fever and very little lymphadenopathy The rash may persist for 4 to 7 days Secondary household cases have been observed A cytopathogenic agent has been reported to have been recovered in roller-tube tissue culture from patients with this disease.

4 *Roseola Infantum* (*Exanthem Subitum*) —(See page 231)—This disease may have an eruption strongly suggestive of rubella It apparently occurs most commonly during the second or third years and in isolated cases, while true rubella is a disease of older children and is uncommon except in epidemics There is usually a three- or four-day period of symptoms suggesting mild influenza, but with a fever which may go up to 103° F or more without sufficient apparent cause and without the child's seeming appreciably ill After three or four days the temperature returns to normal as a diffuse macular eruption appears all over the body, and to a less extent on the head and extremities. This eruption lasts only twenty-four to forty-eight hours In rubella the exan-

1 *Measles.*—A typical case of rubella is easily differentiated from a typical case of measles by the insignificance of the catarrh and constitutional manifestations in rubella, the absence of Koplik's spots, the almost entire absence of fever, the fine macular nature of the eruption, and particularly the changeability of the eruption and the very short course of the disease. The various posterior and lateral cervical lymph nodes may be moderately swollen and tender in measles even as they customarily are in rubella. Very mild cases of measles may closely simulate rubella, and the so-called modified type of measles may be diagnosed only by the history of an exposure to the disease and of a subsequent inoculation with a partially protective serum This modified measles may have the same absence of marked catarrhal symptoms, of Koplik's spots, of much if any fever, and of a protracted course, and the eruption may consist only of small macules diffusely scattered In rubella, however, the eruption is usually quite extensive and out of all proportion to the trifling nature of the concomitant symptoms A history of a previous definite attack of either measles or rubella is of great importance in the differential diagnosis. Authentic second attacks of rubella, as of measles, are quite rare.

2. *Scarlet Fever.*—In symptoms, course, or severity, the average case of scarlet fever has little in common with the average case of rubella, but rubella on its second day may quite strongly suggest a very mild case of scarlet fever where there is little constitutional reaction, only slight fever or sore throat, no strawberry tongue, and only moderate involvement of the skin. In rubella, the eruption is neither constant nor uniform throughout, at one examination it may appear to be erythematous on the face and shoulders, and to consist of scattered macules on the trunk and extremities, but some hours later it may be much more confluent on the extremities and have faded on the face. In most cases the face is especially involved, including the area around the mouth. The rash is of short duration and is followed by only slight desquamation. In contrast to this, the rash of scarlet

fever maintains its punctate erythematous character throughout, and usually lasts from four to seven days. The area around the mouth is notably pale and uninvolved by the eruption, and desquamation is usually a notable feature of the convalescence Leukocytosis is found in scarlet fever, but in rubella there is ordinarily a slight granulocytic leukopenia. The presence or absence of exposure to one or the other disease gives helpful information in the differential diagnosis, as does also a history of a previous attack of either scarlet fever or rubella. The Schultz-Charlton blanching test is positive in scarlet fever.

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4. *Roseola Infantum* (*Exanthem Subitum*) —(See page 231.)—This disease may have an eruption strongly suggestive of rubella It apparently occurs most commonly during the second or third years and in isolated cases, while true rubella is a disease of older children and is uncommon except in epidemics There is usually a three- or four-day period of symptoms suggesting mild influenza, but with a fever which may go up to 103° F. or more without sufficient apparent cause and without the child's seeming appreciably ill After three or four days the temperature returns to normal as a diffuse macular eruption appears all over the body, and to a less extent on the head and extremities This eruption lasts only twenty-four to forty-eight hours In rubella the exan-

them is often the first evidence of ill health, and may last *into the third day. Roseola is only slightly contagious* and in its presence the lymph nodes are not notably involved In each of these two diseases there is a granulocytic leukopenia, with a relative lymphocytosis, more marked in roseola, but plasma cells are more numerous in rubella.

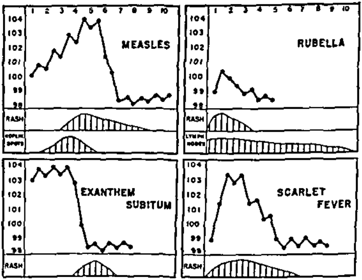


FIG 33 —Diagram illustrating the clinical course of three infectious diseases which may be confused with rubella (Krugman and Ward, J Pediat, *44*, 491, 1954)

5. *Infectious Mononucleosis* —In this disease there may be a faint morbilliform eruption, occasionally slightly papular, widely distributed but particularly on the trunk and in some cases practically indistinguishable from the eruption of rubella There may also be posterior cervical lymphadenitis and leukopenia, but the eruption may last three to seven days, there is usually a more definite pharyngitis, the patient is sicker and for a much longer period, and there is heterophile agglutination.

6. *Intestinal rashes and heat rashes* in infants may cause some confusion, but are usually unaccompanied by even the slight catarrhal symptoms found in rubella, or by adenitis. *Serum reactions* may occasionally cause some question in diagnosis, as may also *drug and sulfonamide reactions* The rickettsial diseases such as typhus fever and Rocky Mountain spotted fever may have eruptions not unlike that of rubella but have much more severe constitutional manifestations.

The accompanying chart from Krugman and Ward depicts graphically the basic differences between the clinical course of rubella and measles, exanthem subitum, and scarlet fever.

THE PROGNOSIS OF RUBELLA

Patients suffering from rubella almost invariably regain normal health promptly, and without complications. Various writers have reported fatal cases, but it may safely be stated either that the deaths were due to concomitant conditions such as an encephalitis or that the patients did not have rubella. The 82 deaths reported from rubella in the United States Army during the First World War were probably due to undiagnosed scarlet fever.

THE PERIOD OF INFECTIVITY OF RUBELLA

If catarrh precedes the exanthem as is sometimes the case the patient is presumably contagious for twenty-four hours or more before the appearance of the eruption. The disappearance of the slight upper respiratory inflammation usually antedates that of the rash, so that the period of infectivity presumably is over by the time the eruption is gone. In confirmation of this, Habel, who had isolated the virus of rubella from the upper respiratory tract during the first forty-eight hours of the eruption, had negative results from nasal washings taken on the third day of the disease He also found viremia in patients bled twelve, twenty-four and thirty hours after the onset of the rash, but not in blood ird day.

ISOLATION AND QUARANTINE FOR RUBELLA

In the light of present knowledge it would seem wise to encourage deliberate exposure of children to rubella so that immunity would be acquired before the childbearing age is reached. Certainly quarantine of all persons with rubella is unwarranted, but every effort should be made to protect pregnant women from exposure to this disease.

IMMUNITY AND THE PREVENTION OF RUBELLA

A true case of rubella is almost always followed by a life-long active immunity, but mild relapses two or three weeks after an attack of this disease have been noted. In *fact, the only method known today of acquiring a lasting* immunity is to have the disease.

Attempts to produce passive immunity by injection of human gamma globulin have been made by many workers. However, the results have been inconclusive, and even those studies which have been well controlled have not afforded definite evidence that gamma globulin is of value in preventing rubella. This statement is true of gamma globulin prepared from pooled normal sera as well as that made from convalescent sera.

Close contact of a pregnant woman with a definite case of rubella in the first trimester presents a serious problem. In the case of a young woman who has no difficulty in conceiving, gamma globulin should be withheld so that possible masking of rubella may be avoided. If the exposed woman is older, and if she has experienced difficulty in becoming pregnant, or if religious scruples against abortion are involved, gamma globulin should be given. In any case, the exposed woman should be observed carefully. If rubella does not occur, the pregnancy should be permitted to go to term. If rubella does develop, then abortion should be recommended to the young woman, provided there are no religious objections and provided that this can be done

without contravening the law. In the case of the older woman, the risk of injury to the baby should be explained, and all aspects discussed with the prospective parents before they are asked to make a decision.

If the contact of the pregnant woman with rubella is a casual one (or if the diagnosis is questionable), the management of the problem should be changed toward a greater tendency to permit the pregnancy to go on.

The dose of gamma globulin recommended for attempted prevention of rubella is 0 1 ml per pound of body weight, the maximum dose being 12 ml.

THE TREATMENT OF RUBELLA

Isolation.—Inasmuch as rubella is usually a trivial disease, and also one which should be contracted during childhood, isolation and quarantine are not recommended, unless possible exposure of a woman in early pregnancy is involved.

Symptomatic Treatment—The only symptom which may need attention is the fever, which when present should cause the patient to stay in bed during its existence and twenty-four hours more

For disinfection, a thorough cleaning and airing of the patient's room is sufficient

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9

Whooping Cough

Synonym.—Pertussis.

Definition.—Whooping cough is an acute, specific, and highly contagious disease involving the respiratory tract, and due to the Hemophilus pertussis of Bordet and Gengou. It is characterized by spasmodic attacks of hard coughing, which end with a characteristic inspiratory whoop and the expulsion of a very stringy tenacious mucus from the trachea.

THE ETIOLOGY OF WHOOPING COUGH

History.—The characteristic symptoms and cause of the disease now known as whooping cough was recognized in the late Middle Ages as an epidemic affliction of children, and De Baillou (Ballonius) in 1578 described an epidemic in Paris of "Tussis Quinta" or "Coqueluche" In 1670 Sydenham described "Infantum pertussis", also called "hooping cough." In the centuries since then, despite the fact that the disease was both endemic and epidemic in many parts of the world, little more was added to the knowledge of the disease until by means of cultural and complement-fixation tests, Bordet and Gengou identified in 1906 the Bacillus pertussis as the specific cause of whooping cough

Exciting Cause.—The Hemophilus pertussis is present in great numbers on the surface of the ciliated epithelium lining the trachea particularly during the catarrhal stage of the disease, and may occasionally be obtained also from lung cultures at autopsy. The only known habitat of this bacillus is in man, and it is pathogenic only for man The Bacillus

pertussis stimulates the formation in a patient's blood of specific agglutinin and complement-fixing antibodies which are usually demonstrable after the second week of the disease, and which, together with the opsonic index, can be of value in the diagnosis of the disease when the clinical manifestations are not conclusive.

Bacteriology —The Bacillus pertussis (also named "Hemophilus pertussis") is a small non-motile Gram-negative bacillus varying from 0.5 to 2 microns in length and usually occurring singly, or occasionally in tandem. It grows best at 37° C. and upon the glycerin-potato blood agar media recommended by Bordet and Gengou, but so also does the Hemophilus influenzæ which it closely resembles morphologically. A definitely acid Bordet-Gengou medium (pH 5) inhibits the growth of the Hemophilus influenzæ and is therefore used for the isolation of the pertussis bacillus, which is subsequently grown pure on the unadjusted Bordet-Gengou medium (pH 6.1 to 5.8). The organisms cannot ordinarily be cultured from the saliva, nor from the sputum unless it has definitely been brought up from the trachea Chievitz and Meyer in 1916 were the first to note that a culture can be obtained by holding vertically the culture medium in a plate a few inches in front of the mouth of a suspected person during a deep cough. Overgrowth with mouth saprophytes may in part be avoided if the child gargles or drinks water just before the plates are exposed. If a voluntary cough cannot be elicited, repeated touching of the posterior pharyngeal wall with a tongue depressor, pressing on the outside of the larynx or deep pressure on the trachea in the suprasternal notch, drinking cold water, laughing, crying, or running may each induce a satisfactory cough. After inoculation, the plate is incubated inverted at 36° rather than at 37° C and on the third or fourth day the minute, discrete, glistening, slightly elevated colonies can be readily seen, particularly with the help of a hand lens, each colony being about 1 mm in diameter and lying in the center of a darkened zone of hemolysis (Fig 34).

In the catarrhal stage of the disease, even from the first

day of cough when the blood count may still be normal, cough droplet cultures are positive in approximately 80 per cent of cases; during the first week of the paroxysmal stage, in about 60 per cent; during the second week, in 30 to 35 per cent; during the third week, in 15 to 20 per cent; and during

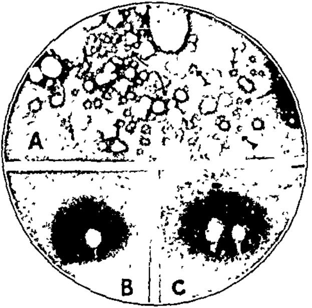


FIG 34 —Cough plate culture of whooping cough bacilli colonies

the fourth week, in 2 to 5 per cent; after the fourth week of the paroxysmal stage the organisms are rarely recovered. Thus at no stage do negative plates exclude the disease.

An improvement on the cough droplet method of inoculating the plates consists of the use of a nasopharyngeal swab made of a piece of soft wire tipped with cotton which, after

pertussis stimulates the formation in a patient's blood of specific agglutinin and complement-fixing antibodies which are usually demonstrable after the second week of the disease, and which, together with the opsonic index, can be of value in the diagnosis of the disease when the clinical manifestations are not conclusive.

Bacteriology.—The Bacillus pertussis (also named "Hemophilus pertussis") is a small non-motile Gram-negative bacillus varying from 0.5 to 2 microns in length and usually occurring singly, or occasionally in tandem. It grows best at 37° C. and upon the glycerin-potato blood agar media recommended by Bordet and Gengou, but so also does the Hemophilus influenzæ which it closely resembles morphologically. A definitely acid Bordet-Gengou medium (pH 5) inhibits the growth of the Hemophilus influenzæ and is therefore used for the isolation of the pertussis bacillus, which is subsequently grown pure on the unadjusted Bordet-Gengou medium (pH 6.1 to 5.8). The organisms cannot ordinarily be cultured from the saliva, nor from the sputum unless it has definitely been brought up from the trachea. Chievitz and Meyer in 1916 were the first to note that a culture can be obtained by holding vertically the culture medium in a plate a few inches in front of the mouth of a suspected person during a deep cough. Overgrowth with mouth saprophytes may in part be avoided if the child gargles or drinks water just before the plates are exposed. If a voluntary cough cannot be elicited, repeated touching of the posterior pharyngeal wall with a tongue depressor, pressing on the outside of the larynx or deep pressure on the trachea in the suprasternal notch, drinking cold water, laughing, crying, or running may each induce a satisfactory cough. After inoculation, the plate is incubated inverted at 36° rather than at 37° C. and on the third or fourth day the minute, discrete, glistening, slightly elevated colonies can be readily seen, particularly with the help of a hand lens, each colony being about 1 mm. in diameter and lying in the center of a darkened zone of hemolysis (Fig. 34).

In the catarrhal stage of the disease, even from the first

imental pertussis has been accomplished with the bacilli alone (as in the classic experiment on their own four sons by the MacDonalds); they are absent in other catarrhal infections, but are present in a high percentage of cases of whooping cough, their gradual disappearance goes hand in hand with the decline in infectivity, and complement-fixing antibodies and agglutinins for the Bacillus pertussis appear during convalescence. Furthermore vaccines properly prepared from suitable whooping cough organisms give a high degree of protection against the disease The evidence appears conclusive that the disease is caused by the Hemophilus pertussis

Manner of Transmission — Since the bacillus can be found in the secretions of the trachea, not only in typical cases but also in mild whooping cough without typical paroxysms, the disease is spread by these secretions, and thus by means of cough droplets by direct contact with recognized and unrecognized cases The disease is thought quite definitely air-borne for short distances Healthy carriers of the infection have likewise been identified but only in members of families in which there was an active case of whooping cough It is probable that the bacillus can be readily carried on the clothes or by other freshly contaminated articles

Season, Sex, Race, and Age. — This disease is fairly prevalent the year round, but there is usually a moderate decrease in the incidence during August, September, and October It is both epidemic in character and world-wide in its distribution The negro apparently has a much higher mortality than the white person, and the incidence is slightly higher in females than in males The vast majority of cases occur in the period from one to five years of age, and the highest mortality is in the first year of life, but no age is entirely immune and in elderly people an attack is a serious matter

THE PATHOLOGY OF WHOOPING COUGH

The Bacillus pertussis which grows on the surface of the mucosa of the respiratory tubes, produces inflammatory

the nose has been cleaned with a preliminary swab, is passed through the nose to touch the posterior pharyngeal wall The swab is kept damp in a rubber-stoppered tube until it can be streaked on a plate If a small loopful of a solution containing 1000 units of penicillin per cubic centimeter is first placed on the culture medium, and the swab is streaked through this drop, the growth of most of the contaminating organisms may be inhibited and a purer growth of the Hemophilus pertussis is obtained, or the antibiotic may be added during the preparation of the culture medium

Whooping cough bacilli vary somewhat in toxin production, morphology, and colony formation, depending on whether they are freshly isolated strains or old laboratory cultures They have also been divided into four agglutinative groups or phases by Leslie and Gardner. The first two phases are toxic to guinea-pigs, whereas the last two are relatively harmless. All cultures freshly grown from patients are the so-called smooth type (which Leslie and Gardner call Phase I organisms); when grown on culture media these bacilli become either the intermediate types (Phases II and III), or the rough type which corresponds to Phase IV. Phase I produces a toxin which is thermolabile, being destroyed by heating to 56° C. for twenty minutes The toxin acts as an antigen because an animal immunized with it will be protected against cutaneous reactions from skin reacting doses of the toxin. Organisms of Phase III and IV have no toxin and vaccines made from them are incapable of protecting against virulent Phase I bacilli.

There is no convincing evidence that toxins *per se* or antitoxins have any effect in the prevention or treatment of whooping cough. In the disease symptomatology, while the exact mechanism of the paroxysm is not known, some observers believe that toxins from bacilli growing on the surface of the mucosa are absorbed and act on the central nervous system which initiates the paroxysm.

The possibility that a virus may play a role in pertussis has been suggested by a number of investigators. But exper-

pneumonia which most often is due to a secondary infection with a streptococcus or a pneumococcus, but which may be due to infection with the Hemophilus pertussis alone. Death, usually due to pneumonia, occurs after three weeks of illness or later. At the autopsy there usually is no significant enlargement of the tracheo-bronchial lymph nodes.



FIG. 36.—Whooping cough. "Eosinophilic" or "anoxemic" degeneration of nerve cells in the hippocampus of the brain. *E*—degenerated nerve cells. (From the collection of Dr. Vera B. Dolgopol.)

The brain of patients dying in convulsions shows congestion and edema of the meninges, occasionally with small subarachnoid hemorrhages. Minute, microscopic hemorrhages are usually scattered in the brain tissue, and nerve cells may show degenerative changes attributable to lack of oxygen ("eosinophilic" or "ischemic" degeneration) rather than a true encephalitis.

changes in the bronchi. The mucosa becomes congested and is infiltrated with lymphocytes and some polymorphonuclears, and the epithelium may desquamate. The mucous glands of the bronchi produce a large amount of stringy mucus which, mixed with some polymorphonuclears, accumulates in the bronchial lumen. It then is propelled into the trachea by the cilia of the epithelium and is expelled by a

A

B



FIG 35—Whooping cough Lung (A)—peribronchial infiltration, (B)—plugged bronchus (From the collection of Dr. Vera B. Dolgopol)

paroxysm of coughing. If the mucus is not completely expelled during the paroxysm, portions of lung tissue may become collapsed (atelectatic).

The mononuclear infiltration from the bronchial mucosa spreads in the tissues surrounding the bronchi producing peribronchial infiltration and peribronchial or interstitial pneumonitis. Both conditions may lead to a true broncho-

pneumonia which most often is due to a secondary infection with a streptococcus or a pneumococcus, but which may be due to infection with the Hemophilus pertussis alone Death, usually due to pneumonia, occurs after three weeks of illness or later. At the autopsy there usually is no significant enlargement of the tracheo-bronchial lymph nodes



FIG 36 —Whooping cough "Eosinophilic" or "anoxemic" degeneration of nerve cells in the hippocampus of *the brain* *E—degenerated nerve* cells (From the collection of Dr. Vera B Dolgopol)

The brain of patients dying in convulsions shows congestion and edema of the meninges, occasionally with small subarachnoid hemorrhages. Minute, microscopic hemorrhages are usually scattered in the brain tissue, and nerve cells may show degenerative changes attributable to lack of oxygen ("eosinophilic" or "ischemic" degeneration) rather than a true encephalitis

The blood picture in the majority of cases of whooping cough is quite characteristic. There is an increase in the total number of leukocytes and a large relative and absolute increase of small lymphocytes; for instance, 20,000 white blood cells with 70 per cent small lymphocytes in a four-year-old child The normal ratio in small children of 1 to 1 of polymorphonuclear leukocytes to small lymphocytes is changed to 1 to 2, or even 1 to 4. This lymphocytic leukocytosis begins late in the catarrhal stage before the cough

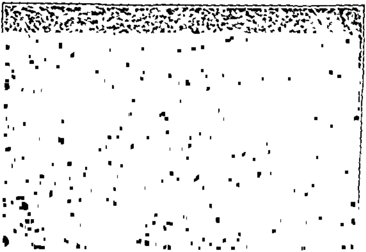


FIG 37 —Whooping cough lung Bronchitis (*A*) peribronchial infiltration, (*B*) beginning desquamation of the bronchial epithelium

becomes characteristic, and so may be of material assistance in the early diagnosis. Occasionally in whooping cough very high total leukocyte counts are found, even over 100,000, thus suggesting the possible diagnosis of a leukemia. However, the lymphocytes in whooping cough are mature and *usually* there is no anemia such as is ordinarily present in lymphocytic leukemia. At autopsy no leukemic changes are found in the organs but the lymphoid follicles of the spleen,

tonsils, etc., may be depleted to exhaustion. For instance, a five-year-old child (W. P. H. No. 5914-1931) who died of whooping cough complicated by a terminal bronchopneumonia had a blood count of 140,000 leukocytes, of which 45 per cent were lymphocytes, yet the autopsy showed no evidence of leukemia.

In uncomplicated whooping cough, the sedimentation rate is normal or even delayed but is increased in the presence of a secondary infection.

INCUBATION PERIOD OF WHOOPING COUGH

The onset of the first sign of ill-health in a case of whooping cough occurs usually some time early in the second week after the exposure. Occasionally it may appear as early as the fifth or sixth day. In general, if no cough has developed by the fifteenth day an exposed child may be considered not infected.

THE CLINICAL MANIFESTATIONS OF WHOOPING COUGH

The symptoms of an average case of whooping cough may be fairly readily divided into three separate and distinct stages (1) The stage of invasion or the catarrhal period, (2) the period of paroxysms; and (3) the period of convalescence.

The Catarrhal Stage.—The catarrhal stage is quite variable in character. It may last from three to fourteen days, and is characterized by symptoms of inflammation of the upper respiratory tract, such as rhinitis and sneezing, a slightly red pharynx with a tickling sensation, a rather tight, dry cough, and sometimes a slight fever and lacrymation. There is also [illegible]

[illegible]

ing with the exception of the tight, dry, hacking cough, to which little attention is paid In the course of a few days the

cough becomes more marked and particularly troublesome at night, but the physical signs of bronchitis are characteristically absent. A tongue depressor lifted slowly off the back of the tongue will occasionally be observed to draw a string of tenacious mucus with it. The rhinitis and fever may disappear after the first week in uncomplicated cases, but the cough persists

Throughout this period, even from the first day of coughing, pertussis bacilli can be obtained in cough droplet cultures or by nasopharyngeal swabs in 80 per cent or more of cases, and after the first few days blood counts will show an increasing leukocytosis with a relative and absolute lymphocytosis.

The Paroxysmal Stage.—The cough begins to appear in separated paroxysms in which there will be a series of from five to ten or more tight coughs during one expiration, followed by a tight sudden deep inspiration with a characteristic crowing sound or whoop. The next expiration is apt to be accompanied by another series of coughs, in turn followed *by an inspiratory whoop, so that a paroxysm may contain* from one to six or eight whoops. The child frequently has a sensation that a paroxysm is approaching and becomes much alarmed, and very restless and apprehensive. During the paroxysm the face is apt to become livid, the tongue protrudes from the mouth, and there may even seem to be a considerable exophthalmos As a result of the coughing, tenacious glairy mucus is usually expectorated, and with it there is apt to be vomited whatever has been eaten recently Strings of mucus hang from the nostrils and lips. As a result of the strain of frequent such attacks, the face may become swollen, puffy and pale with shadows under the eyes. There is a general expression of fatigue and exhaustion, and the entire appearance of the patient, especially of a very little child, is quite pathetic. In older children, however, the general condition between paroxysms is often surprisingly good, and the child may seem normal in every respect.

The paroxysms vary materially in number in different cases One child may be heard to whoop not at all or only once in the course of an entire attack of the disease, and there may be no vomiting at any time. The diagnosis may be presumed from the fact that other children in the family are having typical attacks of whooping cough at that time, or it may be confirmed by culturing the pertussis bacillus from the patient's cough droplets. In fact, in one series there were half as many so-called abortive cases as there were typical instances of whooping cough, the mild atypical cases occurring particularly in older children and in people partially immunized as by vaccine On the other hand, the severest cases may have paroxysms that seem to last a minute or two, and contain six to fifteen whoops or more, and in exceptional cases the paroxysms may occur from thirty to fifty times in the twenty-four hours Paroxysms are usually worse at night, and in stuffy rooms They are usually distinctly less marked if the patient is outdoors Suggestion is of considerable importance in the incidence of the paroxysms If one child in a whooping cough ward has a paroxysm, some of the other children are apt to have paroxysms also, but on the other hand, when a child's attention is absorbed with some plaything, the paroxysms are less frequent Involuntary urination and defecation are not uncommon during severe paroxysms, and prolapse of the rectum is also occasionally met In some cases paroxysmal sneezing has been noted

The duration of the paroxysmal stage is quite variable It varies from one week or less in the very mild cases up to six or eight weeks, and is usually four to six weeks The paroxysms increase in frequency at the start of this period, for perhaps a week, and then remain unchanged in frequency and severity for one to three or more weeks They then become less frequent and less severe, and finally vomiting and whooping gradually disappear

During this stage, cough-droplet cultures of typical cases will reveal the presence of the Bordet-Gengou bacillus but

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portion of cases will show slight bronchitis during the early day of the catarrhal stage, but it is more common to have the physical findings of the chest be entirely normal until the paroxysmal stage has become well developed, at which time the coarse moist râles of bronchitis may be detected. An increase in the severity of the bronchitis is the rule in infants, and the occurrence of a *bronchopneumonia* is all too commonly a resultant complication in inadequately treated babies. It was formerly present in about 20 per cent of hospital cases of whooping cough under one year, a majority of these sick infants dying, but in the past few years the incidence has been lowered by improved methods of treatment to not more than three or four per cent with almost no mortality. Bronchopneumonia is usually due to a secondary infection, but L. W Smith has shown that the Hemophilus pertussis is sometimes the predominating causative microorganism. Bronchial signs may be easily found over a large area or in small scattered patches, or they may not be detectable clinically. Roentgen-ray examination will usually show typical findings, and at autopsy it is not uncommon to find small scattered areas of consolidation in lungs which before death gave practically no physical signs In a small proportion of the cases the pneumonia is lobar in type and caused by pneumonococci An infant weakened by a pneumonia will have fewer and less severe paroxysms than it had before the onset of this complication, or even none at all If the pneumonia clears up, the paroxysms may again become more severe It is quite uncommon for empyema to follow a pneumonia in whooping cough

Atelectasis of a diffuse patchy type is quite common, and the *x*-ray findings may suggest a bronchopneumonia. Although the clinical manifestations may be insignificant, the lesions may last for weeks after the acute stage of the whooping cough

Various other respiratory complications have been reported, such as pulmonary and subcutaneous emphysema, and laryngitis

with rapidly diminishing frequency. The blood serum may show increasing power in agglutination, but this is too uncertain to be of diagnostic value. Complement fixation is high enough to be diagnostic from just before the whoop develops until after the eighth week when a decline develops in the percentage with complement fixation. Most adults who had whooping cough in childhood give negative fixation tests. The blood count may average 20,000 leukocytes with a lymphocytosis, but the count has usually returned to an approximate normal by the fourteenth day of the whooping stage Little laboratory work has been done on abortive cases diagnosed as such by culture

The Convalescent Stage.—The convalescent stage is usually considered to begin at the cessation of vomiting and whooping Patients are apt to have a tight semi-paroxysmal cough for some weeks after the vomiting has ceased, and many children apparently develop the habit of whooping with any cough. In fact, children have been known to whoop for a year or two after an attack of whooping cough, especially whenever they develop a "cold" with cough, and many of these cases have been reported as relapses or recurrences of the disease. Even vomiting may occur with these renewed paroxysms, but the patients are usually non-contagious Their infectivity should be determined by nasopharyngeal swabs or cough-droplet cultures, however.

Accordingly, the entire duration of an average case of whooping cough is usually two or three months. It is occasionally described as three weeks to develop, three weeks to run, and three weeks to fade away, but it would be more accurate to say two weeks to develop, four weeks to run, and three weeks to fade away.

THE COMPLICATIONS OF WHOOPING COUGH

Respiratory Complications.—*Bronchitis* to a slight degree is present some time during the course of most cases, but is usually not enough to affect the temperature. A small pro-

Hemorrhages from the nose are fairly common in whooping cough. Hemorrhage into the skin in the form of purpura or petechiæ has been reported and subconjunctival hemorrhage is quite frequently seen These hemorrhages are mechanical in origin.

In infants who have cut the two lower incisors, an *ulcer of the frenum under the tongue* occurs commonly as a result of the protrusion of the tongue over the teeth during a paroxysm. Some authors stress the presence of such an ulcer as of diagnostic importance.

A tendency to hernia, especially at the umbilicus, may be increased. Enteritis and gastro-intestinal disturbances are apt to complicate the disease in infancy and may be very serious.

Sequelæ.—In addition to the cardiac dilatation and myocarditis that have been mentioned, asthma, emphysema, and bronchitis may appear as sequelæ. Bronchiectasis is a not unusual sequel of severe cases, the commonest cause of this pulmonary disease in children being whooping cough and whooping cough pneumonia. Whooping cough has little effect on well-stabilized primary pulmonary tuberculosis, but active cases may be stimulated to a rapid spread.

THE DIFFERENTIAL DIAGNOSIS OF WHOOPING COUGH

The Bordet-Gengou culture medium can be used for culture plates for cough droplets or for streaking with nasopharyngeal swabs. If a positive report is obtained after about three days of incubating at 36° C the diagnosis is confirmed, but a negative culture does not rule out the presence of pertussis

Typical whooping cough in a sibling, a history of intimate contact with some child in the catarrhal stage, a typical paroxysm or whoop, typical lymphocytosis, and positive complement fixation may all assist in formulating a diagnosis.

Parapertussis resembles mild whooping cough. The two infections can be differentiated solely by bacteriological and

Otitis Media.—Otitis media is always liable to complicate any disease of the upper respiratory tract, and occurs in 10 to 12 per cent of hospital cases of whooping cough. It may be due to the Hemophilus pertussis but is more commonly caused by streptococci. Mastoiditis in whooping cough has always been comparatively unusual, following only 2 to 4 per cent of the untreated cases of otitis.

Convulsions.—Convulsions may occur in whooping cough, particularly in infants and very young children, and are second only to bronchopneumonia as the cause of death in this disease They usually involve the entire body without localizing neurologic signs and are accompanied by loss of consciousness They have usually been attributed to such factors as an encephalitis caused by the toxins of the specific bacillus, or meningismus, or small focal hemorrhages into the brain substance, or to rachitic or gastric tetany (the latter due to an alkalosis induced by the repeated loss of the acid gastric juice through vomiting). A definite encephalopathy may be present with or without the convulsions and if the patient survives, is apt to result in permanent damage

In a relatively large number of children with whooping cough, the spinal fluid shows a moderate increase in pressure, and sometimes in protein content. These changes have been attributed to toxic influences, to mechanical factors of increased pressure during the paroxysms, and to multiple slight hemorrhages as well as to encephalopathy

Other Complications.—*Acute dilatation of the heart,* particularly of the right side, is present during the paroxysmal stage of severe cases, in more instances than is generally suspected The positive pressure of the coughing paroxysms causes increased intra-pleural pressure and increased pulmonary arterial pressure, thus interfering with filling and emptying of the right side of the heart to cause the acute dilatation It is not an uncommong finding in roentgen-ray pictures of the chest in whooping cough, and may be followed by a moderate amount of myocardial damage.

Foreign bodies in the larynx or trachea may cause a spasmodic cough not unlike that of whooping cough, but the onset is usually sudden instead of gradual, whooping and vomiting do not usually occur, and there is no lymphocytosis The roentgen ray may clarify the diagnosis.

Various other conditions such as lingual tonsillitis or lipid pneumonia may more or less simulate whooping cough Croup, whether catarrhal or diphtheritic, may cause a spasmodic cough, but the differentiation should be simple. A paralysis of the recurrent laryngeal nerve will give rise to a paroxysmal cough, but a definite whoop is usually missing, and examination of the vocal cords will reveal a paralysis of one of them.

THE MORTALITY AND PROGNOSIS OF WHOOPING COUGH

The mortality of whooping cough varies most of all with the age of the patient; the younger the patient, the poorer the prognosis It differs from other contagious diseases in that nearly all of the deaths occur in infancy and very early childhood, 85 to 90 per cent occurring before the third year of life In children under the age of twelve months, whooping cough, before the days of the antibiotics and hyperimmune serum, was fatal in 20 to 35 per cent of hospital cases. However, since about 1943 there has been a definite drop in the amount of whooping cough and in its mortality. Of all cases inside and outside the hospitals the average mortality is now but a fraction of 1 per cent but about 100,000 cases still occur annually in the United States

Until recent years in many communities, whooping cough caused more deaths in children under five years of age than diphtheria, measles or scarlet fever, and in children under two years of age more than these three diseases combined. In hospitals it has been nearly as fatal as diphtheria and much more so than measles and scarlet fever (See Table 8) The mortality-rate still increases in mid-winter when broncho-

serological tests and an attack of either disease gives no protection against the other (see page 290).

Bronchitis.—During the catarrhal stage of whooping cough, it is practically impossible to differentiate it clinically from bronchitis When, despite suitable treatment, a cough persists or grows more severe, and particularly when the lung findings are negligible in proportion to the cough, whooping cough should be suspected. A blood count is often quite helpful. In both bronchitis and whooping cough there is apt to be an increase in the total number of white blood cells to between 10,000 and 20,000, but in the former the increase is largely in the polymorphonuclear neutrophils, whereas in whooping cough, the increase is usually in the lymphocytes, a count of 60 per cent being not uncommon. It must be remembered that up to twelve months of age as many as 45 per cent of lymphocytes is normal, the percentage decreasing during the succeeding years to below 30 per cent at ten years

Mucoviscidosis (fibrocystic disease of the pancreas) — Small patients with this disease can imitate the symptomatology of whooping cough in young infants quite closely Half the diagnosis lies in suspecting its presence, and the diagnosis can be confirmed by the absence of trypsin from the duodenal contents

Laryngismus stridulus usually occurs only in small children suffering from rickets or tetany In this disease a crowing sound may be heard during an inspiratory cry which at times sounds not unlike a whoop, but which is due to a spasmodic closure of the glottis, and may be unaccompanied by any cough.

Enlargement of the paratracheal lymph nodes or of the thymus gland may be accompanied by a semi-paroxysmal cough, at times resembling that of whooping cough There is no inspiratory whoop, however, and the attacks are not more frequent by night than by day. The roentgen ray will reveal the enlarged thymus or lymph nodes, or perhaps evidence of tuberculosis.

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pneumonia is most prevalent and in mid-summer when intestinal troubles in infancy are most common In delicate or rachitic infants the outlook is praticularly bad. Children in good homes have an appreciable advantage, such social conditions as poverty and inanition creating predisposing factors whose effect on the patient's general physical well-being may militate against recovery.

TABLE 8 —A COMPARISON OF THE MORTALITY RATES OF WHOOPING COUGH, DIPHTHERIA, SCARLET FEVER, AND MEASLES, FOR ALL AGES

	Willard Parker Hospital			*New York City*		
	No of Cases	*Deaths No*	*Deaths %*	*No of Cases*	*Deaths No*	*Deaths %*
		1935–1939				
Whooping Cough	2503	79	3 12	35,872	488	1 36
Diphtheria	1708	56	3 28	4,761	209	4 39
Scarlet Fever	6774	38	0 56	50,622	204	0 40
Measles	6423	60	0 93	115,386	259	0 22
		1941–1945				
Whooping Cough	3420	57	1 67	28,531	214	0 75
Diphtheria	414	11	2 76	1,514	57	3 76
Scarlet Fever	5592	8	0 14	40,555	41	0 01
Measles	5195	12	0 23	133,452	70	0 05
		1946–1950				
Whooping Cough	2635	22	0 83	12,870	47	0 36
Diphtheria	453	14	3 09	1,102	40	3 63
Scarlet Fever	1487	1	0 07	17,893	4	0 02
Measles	8509	16	0 19	86,740	73	0 08
		1951–1954				
Whooping Cough	1811	9	0 50	7,495	10	0 13
Diphtheria	58	0	0 00	102	4	3 92
Scarlet Fever	758	0	0 00	9,430	1	0 01
Measles	8004	21	0 26	90,413	50	0 06

PERIOD OF INFECTIVITY OF WHOOPING COUGH

Whooping cough is contagious from the onset of the catarrhal stage and the first cough (about the seventh day from exposure) until the paroxysmal stage has reached its maximum, that is, for about the first four weeks of the disease.

It is most contagious when the bacilli are most numerous in the cough droplets, that is, before whooping begins, and thus usually before the diagnosis is made In keeping with the incidence of positive cough-droplet cultures, it has been shown that of cases in children which were caused by exposure to brothers or sisters, about 70 per cent were infected by exposure to the catarrhal stage, about 20 per cent by exposure to the first week of the paroxysmal stage; 8 per cent by exposure during the second such week; and only 2 per cent thereafter

The mild cases, in which there may be little if any whooping, are probably not contagious after the third week

ISOLATION AND QUARANTINE FOR WHOOPING COUGH

In general, a child should be considered exposed if he has been in contact with a patient during the days of catarrh preceding the first whoop or vomiting spell, or at any other time during the disease until three weeks from the onset of the paroxysmal stage Regulations vary in different communities. The younger the children involved the more stringent should be the regulations, as in nursery schools Patients recovering from the disease may, with sufficient safety to their classmates, be allowed to return to school four weeks after the onset of the whooping stage provided that vomiting has ceased, or one week after the last paroxysm that was accompanied by vomiting Children who have previously had the disease or who have received three injections of the vaccine in infancy and a "booster" injection subsequently, may continue in school regardless of any exposure Those who have not had the disease or the vaccine, if exposed at home or on a given definite occasion, as at a children's party, should be excluded from school until fourteen days after the termination of their exposure, while those who have been exposed in school may be allowed with comparative safety to continue at school if inspected and watched daily and if separated from their classmates immediately upon the onset of a fresh cough

IMMUNITY TO WHOOPING COUGH

The newborn are practically devoid of any pertussis antibodies and thus apparently inherit no immunity to this disease, so whooping cough is much more commonly met in the early months of life than are the virus diseases or diphtheria or scarlet fever. Some people appear to enjoy a natural immunity, because they go through life seemingly without ever contracting the disease despite repeated exposure; but it is more probable that they had cases so mild they were not recognized as such One attack of the disease, whether mild or severe is followed by an acquired immunity, which ordinarily lasts for life, but a long-standing immunity may tend to break down when exposure is intimate and prolonged, as when a grandmother undertakes to care for a child with a case of whooping cough So-called relapses or recurring attacks of the disease are usually not due to infection with the pertussis bacillus, and therefore are ordinarily non-contagious, but authentic second attacks with positive cough plate cultures in the second attack at least, have been reported

Of the various pertussis tests for differentiating non-immunes from immunes, Sauer states that the tube agglutination test is trustworthy, and is not very difficult to perform Agglutination in a dilution of 1:320 is considered evidence of immunity

Such tests as complement fixation, and opsonocytophagic tests are also of value in determining the production of immunity but few laboratories are equipped to perform them

PROPHYLAXIS IN WHOOPING COUGH

Passive Immunization.—Young infants being highly susceptible should, when exposed, receive injections of the only specific preventative available, human hyperimmune serum. This serum (serum from a person who has both had the disease and received repeated injections of vaccine) is available

first in the lyophile or vacuum dried form, the equivalent of 20 ml. of serum being dissolved in 10 ml. of sterile distilled water, and second in a globulin fraction, 2.5 ml. of which contains the immune bodies of 25 ml of serum. The repeated intramuscular administration of a 2 5 ml dose is naturally much less painful than of a 10 ml dose The globulin preparation also has the advantage of never containing the virus of serum hepatitis which can contaminate the lyophile preparation. Neither preparation should be given intravenously

The equivalent of 20 ml of hyperimmune serum when given intramuscularly and repeated in three to five days will protect the majority of infants even from a prolonged exposure For most of the others the disease will be greatly modified

Active Immunization *—Vaccines for the prevention of whooping cough have been used for years, having been first listed in New and Non-Official Remedies in 1914 The method of preparation, the contents of the product, and the immunizing result were very variable for years, but in the early 1930's Sauer and others demonstrated that only recently isolated strains of the *Hemophilus pertussis* in Phase I were antigenically potent, although variably so, and from then on whooping cough vaccines became generally used Two types of preparations have been recently available The first was a saline suspended or so-called aqueous vaccine of which a total dosage of 80 billion bacilli divided in three doses and given subcutaneously, was recommended The second was a vaccine treated with an adjuvant, either alum-precipitated, or aluminum hydroxide adsorbed, of which a total dosage of 40 billion bacilli, divided in three doses and given intramuscularly, was preferred if to be given to young infants However there was no suitable standard of potency for these vaccines, and although used very widely in the last fifteen years or so with a very dramatic effect in lowering the morbidity and mortality of the disease, the vaccines protected completely only about 85 per cent of

* Reprinted from Jour Pediatrics, Philip M Stimson, July, 1954

those injected although usually mitigating the manifestations of the disease in those who failed to obtain complete protection

In 1948 a mouse protection test for standardizing pertussis vaccine was adopted by the National Institutes of Health and by the biological manufacturers. The potency was tested by immunizing mice under standard conditions and then in a few days challenging them by the intracerebral injection of exact doses of living pertussis bacilli known to be virulent. The amount of test vaccine required to protect fifty per cent of the mice was compared with the amount required of a standard reference vaccine originally tested for demonstrable protection of children in field trials As an index of potency the "protective antigenic unit" was developed, the value being determined on the basis of the relative mouse-protective or "ED50" values of the test vaccine and of the reference standard.

Hence, beginning in 1953, the potency of all newly prepared whooping cough vaccines must be expressed in terms of "antigenic units," and the total dose of any preparation is 12 units The amount of the reference standard vaccine that contains 12 protective units, contains 96 billion pertussis organisms Fluid vaccines on the market must contain the 12 antigenic units in the total recommended dose and these units must be provided by no more than 96 billion organisms Alum precipitated vaccines, being more antigenic, are limited to 48 billion organisms in the same total dosage of 12 antigenic units

Whooping cough vaccines, whether saline suspended, alum-precipitated, or aluminum hydroxide adsorbed, may be obtained by themselves, or mixed with diphtheria toxoid alone, or mixed with both diphtheria and tetanus toxoids The triple mixtures are in general use, those with an adjuvant

alum cysts. When the injections are started after the sixth

month, the fluid preparations may be preferred and may be given subcutaneously or intramuscularly. Protection in older infants and children may be much more rapid if fluid vaccine is given than if an adsorbed vaccine is used, but in young infants the immunizing response is greater and more lasting following an adjuvant When aluminum hydroxide instead of alum is used as the adjuvant, the actual injection of the vaccine appears to be less painful

For almost all preparations now available, the dose is 0 5 ml. given three times at intervals of at least a month This provides a total of 12 antigenic units. Single recall or "booster" injections of 0 5 ml. each are recommended one year after the completion of the first series, again two years later, and twice more at three-year intervals, or a total of four boosters in the first decade of life Whether to continue the injections thereafter is debatable The degree of immunization obtained may be determined by the pertussis tube agglutination test

The parents should be warned about the possibility of reactions Local reactions consist of redness, tenderness, and induration of varying intensity A nodule may persist for some time at the site of injection In children over two, there may also be systemic reactions of fever and malaise, but sensitization to foreign protein, or susceptibility to the Arthus phenomenon need not be feared Local reactions should not be treated with heat, either dry or wet, but preferably by quiet, and if the reaction be very severe, cool wet dressings will be found comforting. When an injection is followed by an unusually severe local reaction, the dosage for the next injection should be decreased or the injections discontinued

Whooping cough vaccine has caused convulsions, possibly as a result of an allergic mechanism, and a damaging, even irreversible, encephalitis has occurred. This complication has usually been after a second or third injection but may follow the first. Hence the administration of any whooping cough vaccine involves a definite but remote risk of serious

results. However, the mortality of whooping cough can be so high and the protective value of the vaccine is so well established that the truly remote risks should not interfere with wide spread use of the vaccine.

To minimize the dangers, one should postpone injecting a child who is in any way ill, give no two injections at the same site, and discontinue the vaccine for any child who developed a high fever from a previous injection, or any allergic reaction, especially a convulsion. Children with congenital defects of the nervous system may be more susceptible than average to this reaction

The value of having pertussis toxin in a vaccine is not yet substantiated, nor in fact is the rôle of the toxin in the disease yet clearly established. Bacterial pertussis vaccines without toxin produce the proper protective antibodies, *i e.*, agglutinins of Phase I organisms, even as does an attack of the disease itself

The administration of pertussis vaccine to pregnant women, completing the injections one month before delivery, permits the transfer of circulating protective antibodies to the unborn infant by the placenta and may be of value under certain conditions particularly since young infants are ordinarily very susceptible to whooping cough and succumb easily to it However, the duration of the presence of these antibodies in the infants is quite temporary, hardly long enough to make the injection of the mothers worthwhile.

In general, according to Sauer, whooping cough can be eliminated from any community by the following three measures:

1. Early diagnosis with the aid of nasopharyngeal swab cultures and cough plates and a white and differential blood count, with prompt isolation of the patient.

2. Rigid quarantine of non-immune exposed contacts at least through the incubation period.

3 Active immunization of all children as soon after three months of age as possible, with a stimulating or booster

dose of the vaccine at the time of an exposure and before entering school

THE TREATMENT OF WHOOPING COUGH

Specific Treatment.—*Serum* —For severe whooping cough even in early infancy, the administration of 2 5 ml of gamma globulin prepared from the serum of hyper-immunized humans and given intramuscularly in the buttocks every other day for three doses, has appeared to be definitely beneficial A fourth dose may be necessary after five to seven more days.

Vaccines—For the treatment of the disease after the symptoms have once begun, no pertussis vaccine is of accepted value as a therapeutic agent

Drugs —There is as yet no certain specific chemotherapy or antibiotic preparation effective against infection with the Hemophilus pertussis Of the antibiotics in clinical use, the broad-spectrum preparations such as chloromycetin, aureomycin, and terramycin, have the best *in vitro* effect on the Hemophilus pertussis They have not been proven with certainty to be effective in altering the severity and duration of pertussis itself, but they do lower the incidence of secondary infections This latter fact makes the administration of one or another of these remedies definitely indicated for all infants with whooping cough, and such other patients who are having severe attacks of the disease, and some authorities advocate giving penicillin also, particularly to the infants (For dosage, see Chapter 3)

In the symptomatic and supportive treatment of whooping cough, various drugs and preparations have been recommended and customarily used, and many of them have undoubtedly been beneficial when properly administered In the treatment of weak children they should be used only with great caution if at all, and certainly should not be used in the presence of a pneumonia Such sedatives as phenobarbital, beneficial for little children, particularly in pro-

ducing rest at night, are occasionally necessary for older children Ephedrine hydrochloride in 15 mgm. doses has been reported to relieve greatly the paroxysmal nature of the cough, but is apt to cause toxic symptoms.

General Hygiene.—The daily hygiene of the child should be carefully checked and supervised, so that there shall be no constipation, uncleanliness, fatigue and excessive loss of sleep, or lack of fresh air, to militate against the child's chance of a normal recovery.

General Treatment.—Mild cases of whooping cough will run their course without very great disturbance to the patient, even though there be no medical treatment whatever, but when a case is severe the treatment given may not only make the patient vastly more comfortable, but may be the determining factor whether or not the patient survives the disease

As soon as the diagnosis is suspected, the patient should be promptly and effectively isolated from all susceptible people. If fever is present, as is frequently the case during the catarrhal stage, the child should be put to bed and kept there for the duration of the fever and two or three days more. It is wise also from then on to take the temperature of the child at least once or twice a day until convalescence is well established, so that the reappearance of fever, indicating *some complication, may be detected at its onset.* If circumstances and the weather permit, the older child's bed should be outdoors Whooping cough patients are usually more comfortable and less likely to have paroxysms while outdoors in the fresh air than when indoors, but if bronchopneumonia or an appreciable amount of bronchitis is present the air must be at least 70° F. in warmth. If patients are up and about, it is desirable to allow them to be outdoors, but great pains should be taken to keep them well away from other children who have not had whooping cough When four weeks have elapsed since the onset of the whooping and vomiting (some authors say three weeks) this isolation may be relaxed unless the vomiting is still of frequent occurrence, in which case if only for esthetic reasons, isolation should be continued until there is no further vomiting.

The diet in whooping cough is frequently of very great importance. In general, frequent small meals are less apt to be vomited than infrequent large meals. After a paroxysm accompanied by vomiting, there is often a latent period during which a moderate amount of food will be readily taken and retained by the patient, particularly if the mouth is first washed out with some pleasant tasting preparation containing a little sodium bicarbonate. For infants, concentrated foods, such as thick cereal feedings, are usually better retained than dilute formula preparations and because of the unfavorable influence of rickets on the prognosis, vitamin D should be stressed. Vitamin C in doses of 150 to 200 mg a day has been reported as apparently shortening materially the whooping stage and relieving the paroxysmal symptoms For many older children the foods that are eaten seem to make little difference in the vomiting, while there are other children who appear to vomit invariably after eating certain foods One boy, aged nine years, who had his whooping cough in May and June always had a severe paroxysm with copious vomiting after eating strawberry shortcake Where the vomiting is frequent and there is a resultant loss of appetite or dread of eating, an acidosis may occur to lesser or greater extent, and should be guarded against by restricting the intake of fats and by giving the carbohydrate type of liquids such as fat-free broths, gruels, glucose solutions, and orange juice Lollipops for older children will occasionally be found both very welcome and advantageous If the vomiting is unusually persistent, gastric lavage with 0 5 to 1 per cent solutions of sodium bicarbonate in warm water will be found efficacious in removing accumulations of swallowed mucus, and if done at intervals of twenty-four to forty-eight hours may appreciably diminish the vomiting

Small infants with coughs too weak to raise the mucus from their tracheas, can be greatly benefited by repeated pharyngeal and laryngeal suction using a soft rubber catheter, followed by placing in an oxygen tent provided with moist oxygen Together with hyperimmune serum, these

measures have saved many babies desperately ill with whooping cough

During a severe paroxysm a child can often be materially helped by the attendant's getting behind the patient and placing both hands firmly over his abdomen, or one hand there and the other on his forehead, holding the head over a basin A glass of sodium bicarbonate (1 teaspoonful) and water should be kept at hand, so that the attendant can wrap a soft cloth around a finger, dip it in the solution, and assist the child in cleaning the stringy mucus from the mouth and pharynx

Roentgen-ray treatments have been advocated for reducing the severity and frequency of the paroxysms and of the vomiting, but probably are of little if any benefit. The ultra-violet ray has also been advocated for relieving the paroxysms and increasing the appetite The occasional inhalation of 7 per cent carbon dioxide mixed with air or oxygen has been advocated by Henderson to keep the lungs sufficiently clear as a result of deep breathing, so that the paroxysms may be diminished in frequency and intensity and the tendency to pneumonia may be reduced.

Patients suffering from severe attacks of whooping cough are peculiarly in need of sympathy and comforting, and a kind nurse can be of very great benefit.

Treatment of Complications —Bronchopneumonia in whooping cough is almost always extremely severe Because it may be due to the Hemophilus pertussis itself or to a secondarily invading virus, it does not invariably respond well to the sulfa drugs or to antibiotics, although they are effective against the usual pneumococci and streptococci. Pulmonary [illegible] that

prolong the course of the illness When large segments [illegible] lobe become atelectatic, the use of bronchoscopy must be considered, and when spontaneous resolution of the atelectasis is delayed or prolonged over three or four weeks, bronchoscopic treatment with suction may be required

In small infants, pertussis pneumonia may be accompanied by myocardial damage as evidenced by a rapid pulse rate, poor heart sounds at the apex, by a gallop rhythm, and by electrocardiographic changes When it is considered that the injury to the myocardium has become serious, some such digitalis preparation as digitoxin is recommended. The total dosage by mouth spread over twenty-four to thirty-six hours for digitalization by this preparation is 0 03 mgm per pound of weight for infants under twelve months, 0 02 mgm. for those from one to two, and 0 01 mgm per pound for those over two years. The sustaining dose is about a tenth as much in each twenty-four hours It can be obtained in scored tablets containing 0 05, 0 10, 0 15, and 0 20 mgm each, as well as in solution form for hypodermic or intravenous injections, which are rarely necessary

For digoxin, which is preferred to digitoxin by some, the dose for infants under one year of age is 0 075 mgm per kilo per day or 0 35 mgm per pound The dose is the same whether given intramuscularly or by mouth, and the daily maintenance dose is 25 to 30 per cent of the above digitalizing dose

The child should be kept warm, and the air that the child breathes should not be colder than 65° or 70° F , but it should always be fresh Especially in small infants, dyspnea and cyanosis may be severe, and frequently require treatment with oxygen Counterirritation to the chest may be quite beneficial, and perhaps can best be obtained by shining a heat lamp on the skin, thereby giving heat without weight Various stimulants such as caffeine and particularly oxygen and transfusions may be necessary

Convulsions may be relieved by the use of phenobarbital, but it is sometimes necessary to give sniffs of chloroform before relaxation is obtained In aggravated instances lumbar puncture with release of pressure of the cerebrospinal fluid may be necessary Chloral in repeated small doses given in 30 to 60 ml o fwarm milk by rectum may prove advantageous Cyanosis accompanying convulsions should

be treated by the administration of oxygen. In view of the fact that the convulsions in whooping cough may at times be due to tetany, calcium and vitamin D should be given each infant suffering from whooping cough to prevent this possible complication.

Treatment of Convalescence.—In most instances, after a severe case of whooping cough, a prolonged vacation in the mountains or at the seashore is very desirable, and general tonics such as those containing the vitamins are beneficial Plenty of good nourishing food and much sleep are to be stressed

PARAPERTUSSIS

This disease is caused by Hemophilus parapertussis. It closely resembles mild pertussis, from which it can be differentiated by bacteriologic methods only. H. parapertussis was first isolated from patients believed to be suffering from whooping cough in 1937 by Eldring and Kendrick, Bradford and Slavin in the United States. H. parapertussis is morphologically indistinguishable from H. pertussis. The two organisms can be differentiated, however, by cultural and immunologic methods Cross agglutination between the two organisms occurs, due to a common minor antigen. Specific antibodies against H. parapertussis are of frequent occurrence in the sera of children. This suggest that parapertussis may be a common disease, which often goes undiagnosed Lautrop showed that parapertussis agglutinins were present in a very large percentage of the population in Denmark, having been found in the sera of 76 per cent of children eleven years of age (only 6 per cent were positive in the first year of life).

An attack of pertussis or of parapertussis does not protect the patient against the alternate disease, and vaccination against pertussis does not confer immunity against parapertussis.

The incubation period of parapertussis is probably from six to fifteen days. Onset may be more abrupt than that of

pertussis. The cough is spasmodic, and may be followed by a whoop and by vomiting, but it is less severe than the cough of pertussis. The disease usually lasts from one to three weeks and complications are rare. Parapertussis encephalitis has not been reported Only two deaths due to parapertussis have been recorded

Treatment is symptomatic Severe cases may be treated with antibiotics, of which chloramphenicol (chloromycetin) seems to be the most effective. The patient should be isolated

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10

Mumps

Synonym.—Epidemic parotitis.

Definition.—Mumps *is an acute contagious disease* caused by a virus and characterized usually by swelling and tenderness in one or more of the salivary glands (particularly the parotids), by comparatively mild constitutional manifestations, and by a tendency to involve other glands and the *central nervous system.*

Mumps may primarily be an infection of the blood stream by a virus which has a predilection for the salivary glands, the pancreas, the mature testicles and ovaries, and the brain, the most susceptible but not invariable points of localization being the salivary glands. For example, apparently well established cases of mumps meningo-encephalitis are on record without recognizable involvement of the salivary glands (Montgomery).

THE ANATOMY OF THE SALIVARY GLANDS

The normal human being has 6 salivary glands, 3 on each side, named the right and left parotid, submaxillary, and sublingual glands

The parotid gland is an irregularly shaped mass roughly $1\frac{3}{4}$ inches by 1 inch by $\frac{1}{2}$ inch. It is situated laterally to the angle of the jaw and extends from the level of the external auditory meatus above to the lower margin of the ramus of the jaw below, and from an anterior point about a third of the way from the angle of the jaw to the point of the chin, backwards beyond the angle of the jaw to form a *tail below*

the ear with its posterior and inferior border resting on the upper surface of the sterno-cleido-mastoid muscle. It is drained by Stenson's duct, which runs forward in the soft tissues of the cheek to a very small orifice at the top of a

The submaxillary gland is somewhat similar in size to a small walnut, but with three flattened sides, and is placed medially and anteriorly to the angle of the lower jaw, and below it. It is thus partly under cover of the mandible or jaw bone. It is drained by the submaxillary or Wharton's duct, which runs forward through the soft tissues under the side of the tongue, and then under the mucous membrane to a small orifice just to the side of the mid-line, on the summit of a soft papilla in the frenum under the tongue

The sublingual gland is almond-shaped and about twice the size of an almond. It is situated beneath the mucous membrane of the floor of the front of the mouth, just to the side of the mid-line, and is drained by a number of small ducts which leave the upper part of the gland and open in a series of papillæ which are placed along the summit of a ridge in the mucous membrane, the plica sub-lingualis, which in turn is caused by the presence of the gland just beneath. Wharton's duct is buried immediately posterior to this ridge

THE ETIOLOGY OF MUMPS

Exciting Cause and Bacteriology.—The specific etiological factor in mumps is a filterable virus which is present in the secretions from the nose and mouth, and which is usually communicated by direct contact. In some cases and perhaps in every case, the virus is carried in the blood stream at some time in the course of the disease Besides in the saliva and blood, the virus has also been found in the spinal fluid of human beings with mumps infection of the central nervous system It has been found there as late as the sixth day of

an encephalitis, and also occasionally in the saliva of patients with meningoencephalitis but without apparent involvement of the salivary glands The infection is not readily carried by a third person

Johnson and Goodpasture obtained the virus from cases of mumps in man, transmitted it through several generations of monkeys and then reproduced the disease in susceptible human volunteers. The virus is also transmissable to hen's egg embryos Purified virus varies in size from 85 to 200 millimicrons The virus may be kept in the frozen state for



FIG 38 —Mumps, involving the parotid, submaxillary, and sublingual salivary glands on the patient's right, and only the parotid on the left—an unusual combination

long periods with little loss of potency When kept at $-20°$ C it remains infective for at least four years. The virus remains potent also when vacuum dried from the frozen state. No antigenic differences have yet been discovered between the rather small number of strains that have been compared with one another.

Season, Sex, Race and Age.—The disease is endemic in large cities, but frequently occurs in epidemic form. Sex, race, and climate apparently have no bearing At the British Military Hospital for contagious diseases at Rouen in 1918,

there were at the same time in one mumps ward, men from eleven different nations. The sickest patients were a Chinese laborer and an American sergeant of aviation More epidemics of mumps occur in winter and spring than at other times of the year. Children between the ages of five and fifteen years form the large majority of the patients, but mumps may occur at any age, although it is uncommon in the first half year or after the fortieth

THE PATHOLOGY OF MUMPS

Owing to the fact that deaths never occur during the course of mumps except from some intercurrent condition, opportunities to study the anatomy of the salivary glands during the course of this disease have been very few. Virchow described an inflammatory, serous, and cellular infiltration of the intra-acinous and peri-acinous ducts In addition to involvement of the glands there is apparently also congestion and edema of the surrounding connective tissue A lymphocytic meningoencephalitis often develops during mumps, but is never fatal A pure encephalitis *per se* is a more infrequent complication, but deaths during this complication are exceedingly rare. The few cases that have come to autopsy have shown cuffs of lymphocytes around the blood vessels of the white matter

Johnson and Goodpasture showed the pathology in the parotid gland of monkeys to be edema of the gland and surrounding tissue with pinpoint hemorrhages in the capsule Destruction of cells throughout the parenchyma, and infiltration with monocytes and lymphocytes were also noted.

In the blood there is customarily a reduction of the number of polymorphonuclear leukocytes leading to a relative increase in the lymphocytes. If orchitis develops there is usually a change from lymphocytosis back to polymorphonuclear leukocytosis

The blood diastase is increased markedly above a normal of 75 to 150 mg The erythocyte sedimentation rate is not affected in uncomplicated cases

IMMUNITY TO MUMPS

There is probably a congenital immunity to mumps which lasts from four to six months, present only if the mother has had mumps The disease has been reported in the neonatal period secondary to cases of mumps in the mothers around the time of labor (von Reuss) One attack of the disease confers an acquired immunity, which usually is permanent, even though but one salivary gland be involved. In very rare instances a child may have a second attack, and we have seen mumps of the right parotid alone in a seven-year-old girl followed three months later by mumps of both parotids and both submaxillary glands On the other hand an infection with mumps virus may be so mild as to produce no recognizable clinical manifestations and such clinically inapparent infections confer immunity as effectively as does an overt attack.

THE INCUBATION PERIOD OF MUMPS

Mumps is apt to develop during the third week after exposure, especially on the sixteenth to eighteenth days, but the exact number of days of the incubation period is rather variable The probable outside limits are twelve to twenty-four days.

THE CLINICAL MANIFESTATIONS OF MUMPS

During the period of incubation there are ordinarily no manifestations of ill health. The period of invasion may last from twelve to twenty-four hours before the involvement of a salivary gland is apparent During this time there may be a slight fever and some chilliness with a certain amount of general malaise and dizziness. Pain in or behind the ear, and sore throat are quite frequent complaints, but on analysis the latter proves to be pain on chewing or swallowing rather than due to an actual pharyngitis. In many cases these

prodromal symptoms may be entirely absent, the first evidences of ill health being tenderness, pain, and swelling, involving one or more of the salivary glands.

One or both parotid glands are involved in nearly every case. When both parotids are affected, the process usually begins in one gland from one to three days before it is noted in the other gland, but both glands return to normal around the eight day. Quite commonly a parotid and a submaxillary gland on the same side are involved together, in which

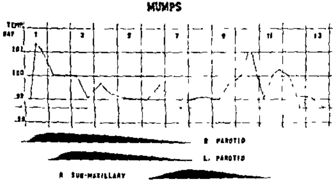


Fig 39 —Showing a moderately severe case of mumps in a boy aged our years The fever on the tenth and eleventh days was considered due to a mild catarrhal otitis media

case the general swelling is very extensive We have seen one patient in whom apparently all 6 salivary glands were involved, and one other patient in whom only the sublingual glands were involved. The disease, however, is apt to involve only the parotids or perhaps both parotids and one submaxillary.

When the parotid is involved, the swelling and tenderness are usually very noticeable immediately below the external ear, and just anterior thereto; as the swelling becomes more marked, it extends out onto the cheek, down below the angle of the jaw, and behind to the tip of the mastoid bone, and a

finger passed backward along the ramus of the jaw can usually detect quite easily the anterior margin of the swollen parotid gland. When the submaxillary gland is involved, the swelling down into the neck is much more extensive. Involvement of the sublingual gland is accompanied by swelling below the tip of the chin, and to one side or the other of the mid-line. The skin over the swollen glands retains a normal color, but may become tense and shiny. The first one to three days, the glands are quite tender, fairly soft to the touch, and somewhat painful, but after that the swelling is usually unaccompanied by much discomfort, if the face is in repose. Mastication is often accompanied by more or less discomfort, and swallowing, particularly of acid substances such as those containing vinegar or lemon juice, is apt to aggravate the pain.

The duration of the swelling in mumps is usually seven to ten days In a given gland the swelling usually reaches its maximum on the second day. After the fourth or fifth day it begins to subside fairly rapidly, and the appearance of the face is usually normal before the tenth day. However, occasionally the swelling will last into the third week, and instances have been reported where it has lasted a number of weeks. Abscess formation in a gland affected by mumps does not occur without secondary infection.

Ducts of involved glands are apt to show a slight area of inflammation around their orifices. The papilla at the opening of Stenson's duct is occasionally found to be puffy with a red spot in its center at the opening of the duct; and Wharton's duct can occasionally be noted as swollen, and redder than usual. In some cases the salivary secretions may be reduced in amount, and the mouth becomes unusually dry. The pharynx is ordinarily normal in appearance.

Aside from the involvement of the salivary glands, other symptoms of the uncomplicated disease are few. Fever may be absent throughout the course of the disease, or it may vary up to as much as 103° F. or more for two or three days. It occasionally appears twenty-four hours before the swelling.

and usually has subsided in three or four days. Headache, malaise, and anorexia may be present the first few days During the last two or three days of the swelling, unless some complication intervenes, there is customarily no evidence of ill health other than the involvement of the glands, so that it is often difficult to persuade patients to remain in bed during this period.

A complement fixation test for the serologic diagnosis of mumps has been developed by Enders and his associates, using an antigen consisting of a dilute suspension of heat-inactivated virus obtained from the parotid glands of monkeys suffering from mumps. More recently, antigens prepared from virus infected eggs have been used quite universally The complement fixing antibodies in the serum of suspected cases are tested early during a disease and again shortly after recovery. If there is any rise in titer, the patient must at least have been exposed to the virus and been stimulated by the infection, latent or obvious, to produce the increase in antibodies. Complement fixation is often positive by the seventh day of the disease and almost always by the fourteenth day. It may become negative again in six to twelve months, or the complement fixing antibody may persist for years although at very low levels

Immunity or susceptibility may also be determined with reasonable accuracy by means of a skin test which is performed by injecting intradermally 0.1 ml of an inactivated suspension of virus obtained from infected egg embryo, similar to the vaccine material only more dilute (page 308) A reaction less than 11 millimeters in diameter after twenty-four hours is considered negative A positive skin-test indicates past invasion by the mumps virus, and also indicates a state of resistance to the virus. While the skin-test is of value in determining the state of immunity to mumps, it is of little use as a diagnostic aid because it may not become positive until two months after the onset of the mumps Furthermore, injection of the skin-test antigen may give rise

to antibodies which would interfere with interpretation of complement fixation tests.

By means of serologic and skin-tests it has been estimated that 20 to 40 per cent of mumps infections are inapparent or subclinical

THE COMPLICATIONS OF MUMPS

With the exception of meningo-encephalitis, complications of mumps are quite unusual before puberty After that period they are quite common; in fact, these manifestations are considered by some as part of the systemic disease rather than as complications They usually appear after the first five or six days of the involvement of the salivary glands However, they may occur prior to, coincidental with, or even without, such involvement

1. **Orchitis.**—When adult males are attacked by mumps an orchitis occurs in about one-fifth to one-fourth of the cases, but it rarely is present before puberty. This complication usually begins about the seventh day of mumps, but may occur any time between the third and eighteenth days. It is usually ushered in by a sudden high fever, with much prostration and general malaise, and sometimes vomiting and considerable headache Perhaps not until six to twenty-four hours later, will one of the testicles become painful, tender, and appreciably swollen. This local condition becomes rapidly worse, so that in the course of another twenty-four hours the affected testicle will be two or three times the size of the unaffected gland The swelling and inflammation usually last four to seven days, subsiding at the end of this period to complete disappearance of the tenderness, and usually a size that is rather smaller than normal. This atrophy is liable also to be accompanied by partial loss of function of the gland, but complete sterility as a result of mumps is quite unusual.[1]

[1] WERNER Ann Int Med, 32, 1066, 1950

The epididymis is involved with the testicle in the inflammation and swelling, and the involvement is ordinarily of one gland only, but both sides are involved in about one-sixth of the cases of orchitis, either together or consecutively The condition is usually very distressing to the patient, not only from the immediate physical discomfort which is very considerable, but also from the fear of the loss of function On this latter point he should speedily be reassured since sexual function is usually maintained after an orchitis in mumps

2. **Pancreatitis.**—Toward the end of the first week of the disease a general inflammation of the pancreas may occur. The symptoms are usually sudden in onset with marked prostration, severe and persistent nausea and vomiting, considerable epigastric tenderness, a variable amount of pain in the upper left quadrant of the abdomen, and in most instances constipation. If the pain is as low as the neighborhood of the umbilicus it may be difficult to rule out appendicitis. The urine remains sugar-free The symptoms last usually four to seven days, gradually diminishing, and the patient makes a complete recovery

While a pancreatitis complicating mumps occurs most commonly in women, it may attack men, but it rarely occurs before puberty. However, of three children with mumps in one family, an eleven-year-old boy on the sixth day of his illness developed symptoms of pancreatitis, with fever, vomiting and considerable left epigastric tenderness, and his nine-year-old sister did likewise on the ninth day of her mumps. She vomited nearly everything for six days, and both children for a week or more did not like to lie on their left sides because of tenderness in the region of the pancreas

3 **Inflammation of Other Glands** —Inflammation of other glands, such as the thyroid, the mammary and lacrimal glands, the ovaries, and the prostate, has been reported, but is quite uncommon, with the possible exception of that of the ovaries, a condition usually difficult to diagnose but which

may occur in 5 per cent of cases in adult females, together with pain in the breasts and external genitalia

4. **Involvement of the Central Nervous System.**—Mumps is much the commonest of the contagious diseases to be complicated by an encephalitis, and a mumps encephalitis, being usually a meningo-encephalitis, is the least severe of all the forms of encephalitis It usually occurs during, or several days after the parotitis More rarely it may precede the glandular manifestations, or in about half the cases there may be no apparent involvement of any salivary gland. The diagnosis is then suggested by the relationship of the encephalitis to such manifestations as orchitis or to the occurrence of other and more typical cases of mumps, and is confirmed by complement fixation tests made during and also subsequent to the encephalitis manifestations An increase in titer of mumps complement fixing antibodies can be caused *only by the mumps virus*

In many instances a transient period of headache with slight fever for two or three days constitutes the only evidence of an encephalitis, but the more marked cases are characterized, as in encephalitis due to other causes, by fever, severe headache, vomiting, and often delirium and coma, and by the customary evidences of meningeal irritation, such as rigidity of the neck and a positive Kernig's sign After three or four days the manifestations of encephalitis ordinarily disappear and the prognosis is excellent for complete recovery The spinal fluid shows increase of pressure and usually of total protein to well above 30 mgm., normal amounts of sugar, and a cell count of 50 to 1000 cells, mostly lymphocytes In one series, the spinal fluid has been found abnormal in 40 per cent of successive cases of mumps

Various forms of neuritis have been described, especially [illegible]

ringing in the ears. The cause of this distressing complication is still undertermined, but it is probably due to some

disease of the labyrinth and the terminal fibers of the auditory nerve. There is loss of bone conduction and the deafness unfortunately may at times be permanent despite all treatments.

Other complications reported include a self-limited arthritis, also pericarditis and myocarditis, occurring apparently only in adults, and all comparatively rare. Acute nephritis has been observed in a few instances, but the relation of this complication to mumps has not been established with certainty.

THE DIFFERENTIAL DIAGNOSIS OF MUMPS

1. *Other Affections of the Parotids.*—Secondary infections of the parotid glands occasionally occur in any infectious disease, often going on to suppuration. They may be secondary to septic conditions of the mouth, or they may occur in such diseases as scarlet fever, diphtheria, pneumonia, typhoid and typhus fever. Similar involvements of the parotids may follow various abdominal operations or inflammations. In many of these circumstances, pus may be squeezed out of the opening of Stenson's duct, and the blood count usually shows a leukocytosis in contradistinction to the slight lymphocytosis which is customary in mumps. Mumps must also be differentiated from Mikulicz's syndrome, which is characterized by rather chronic enlargement, not only of the salivary glands, but often also of the lacrimal gland, and in which there is customarily no fever. Benign and malignant tumors may also occur in a salivary gland, and must be ruled out in the differential diagnosis.

Mumps may also be confused with recurrent parotitis. Since true second attacks of any such virus disease as mumps are rare, second attacks of parotitis should be considered due to some cause other than infection with the mumps virus. Third and fourth attacks of parotitis are certainly not mumps, in most such cases bacteria are responsible for the inflammation, and isolation of the causative organism from Stenson's duct usually establishes the correct diagnosis.

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Various forms of neuritis have been described, especially involvement of the facial nerve. In a small number of cases, deafness occurs toward the end of the first week, and usually comes on suddenly, perhaps after some slight dizziness and ringing in the ears. The cause of this distressing complication is still undertermined, but it is probably due to some

swelling of the salivary glands. A girl in school Friday morning whose mumps was first noticed Saturday morning gave the disease to 5 of 16 susceptible classmates. The disease is apparently most easily transmitted during the first three days. In one experiment, in 15 children exposed to a preparation of mumps virus, the virus could be isolated from the saliva of all beginning on the eleventh to fifteenth day after exposure, and for one to nine subsequent days. Six developed clinical mumps, 1 an orchitis only, and 8 had inapparent infections proven serologically. In those with clinical mumps the virus was isolated from the saliva until the fourth day only of the disease.[1]

Mumps is a little less contagious than measles, whooping cough, and especially chickenpox, but is definitely more so than scarlet fever or diphtheria.

ISOLATION AND QUARANTINE FOR MUMPS

In most communities there is no actual quarantine for mumps, but isolation of patients is advised. Opinions differ as to the length of time necessary for such isolation, but it has been found safe to allow children to return to school one day after the complete disappearance of the swelling of the salivary glands. Adult males should be isolated until the swelling of an orchitis has subsided, or until the liability of the development of an orchitis has passed, which is usually a week after the subsidence of the parotitis.

Children should be considered exposed if they have been in contact with patients during the twenty-four hours preceding the appearance of the swelling, or during its presence.

Children who have had the disease may continue at school. All children who have not had this disease should be considered susceptible and their parents should be notified in case they also are susceptible. In particular, a father may want to take measures to avoid exposure to his child at the time she may be developing this disease. Susceptible chil-

[1] Enders, *et al.* J. Exper. Med., 88, 223, 1948.

2. *Calculus.*—A calculus or a plug of inspissated mucus may develop in Stenson's duct, or more commonly in the duct of the submaxillary gland, and as a result of the obstruction, intermittent swelling of the affected gland may occur, particularly when the stimulus of food gives rise to active secretion of saliva.

3. *"Swollen Glands."*—It may be impossible to differentiate in appearance swollen lymph nodes of the neck, particularly those around the angle of the jaw, from mumps of the submaxillary salivary glands alone. Mumps of a parotid gland should be easily distinguished from a cervical lymphadenitis by the location of the swelling which in mumps is anterior to, as well as below, the ear, and closer to the ear than is the case with lymphadenitis. Palpation of a fairly definite anterior margin of the swollen parotid and redness around the opening of Stenson's duct also facilitate the diagnosis. A swelling of the lymph node that is situated on the center of the parotid anterior to the external ear may at times cause confusion.

Mumps encephalitis can be differentiated from acute lymphocytic choriomeningitis, and other forms of encephalitis including polio encephalitis by repeated complement fixation tests using a mumps virus antigen.

THE PROGNOSIS OF MUMPS

Uncomplicated mumps is never fatal, and even when complications occur, the eventual outcome is ordinarily an early return to normal health. Partial atrophy and perhaps some diminution of function are apt to follow involvement of a testicle, but actual sterility as a result of mumps is certainly rare. Should impairment of hearing have occurred, this unfortunate condition may become permanent.

PERIOD OF INFECTIVITY OF MUMPS

This is ordinarily considered to be from twenty-four hours before the appearance of symptoms until the subsidence of all

or so rather than during adolescence or later. Nevertheless even early in life such distressing complications as pancreatitis may occur. Hence the deliberate exposure of susceptible children, as advocated by some, should be considered guardedly and not lightly undertaken, particularly if their fathers have not had mumps and might in turn be exposed

THE TREATMENT OF MUMPS

The antibiotics are of no proven value in the treatment of mumps virus infections, nor is there any specific remedy of recognized merit. Serum preparations are of preventative value only. Diethylstilbestrol in doses of 5 mgm by mouth one to three times daily has been thought to lessen the discomfort particularly of orchitis, and perhaps to shorten the fever

Children with mumps should be kept in bed as long as there is any fever and twenty-four hours more. Adults should stay in bed as long as there is any swelling of a gland and if this period is comparatively short, two or three days more. It has been thought possible that this long stay in bed has a protecting influence against the distressing complications of orchitis of men and pancreatitis in both sexes, but this hypothesis has not been substantiated In women this prolonged rest may ameliorate the dysmenorrhea which is otherwise liable to happen should a menstrual period occur during an attack of mumps

Discomfort due to the inflammation of the salivary glands may usually be relieved by warmth, such as a hot-water bottle or an electric pad applied to the cheek, but many patients derive more comfort from an icebag A warm cloth tied snugly around the face with a bow on top of the head is usually found to be most comforting, not only for its warmth but especially for the support it gives to the heavy cheeks

The usual care of a patient with an infection should also be observed, such as attention to proper elimination, the ingestion of extra fluid, and especially cleanliness of the

dren who have been exposed at school or elsewhere than at home may usually be allowed to continue at school, if from the fourteenth to the twenty-second days after the exposure they are examined daily by a parent at home or by the school physician Where exposure has occurred in a family, it is usually fairer to the school if after being allowed to return to school on the third day after the appearance of the patient's swelling, the exposed susceptible children are excluded from the fourteenth day after the first exposure until the twenty-second day after the last exposure

PROPHYLAXIS IN MUMPS

Normal gamma globulin is of no value in the prophylaxis of mumps, but gamma globulin made from pooled mumps convalescent serum if available might prove of some prophylactic value

For active immunization a vaccine made of virus prepared from the allantoic fluid of infected chick embryos and inactivated either by ultraviolet light or by formalin is of some value in building up an immunity in skin-test negative individuals It significantly increases the amount of complement fixing antibodies in two or three weeks although by itself it may not produce a positive skin-test Recent evidence indicates that the vaccine may decrease the incidence of mumps if given very soon after exposure At present it should be given only to adult males with a negative skin-test who have been recently exposed to the disease The dosage is 1.0 ml. given intramuscularly as soon as possible after exposure and repeated one week later The vaccine should not be given to persons who are allergic to egg, chicken, or chicken feathers.

Isolation of the patient should be practiced in every case.

ferable for a child to have the disease when ten years of age

mouth and to give glucose and saline solutions intravenously or possibly by rectum.

A mumps encephalitis especially if mild need be treated only by sedation, a lumbar puncture being necessary only to bring possible relief for a severe headache or to furnish added evidence when the diagnosis is not obvious.

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mucous membranes of the nose and mouth. For general malaise, aspirin may be used

Adult males in the first days of parotitis may be given 40 to 50 ml. of hyperimmune or convalescent mumps serum intravenously if obtainable. This has been shown to cut the incidence of orchitis to 16 per cent in one series while a control group showed an incidence of 28 per cent (Rambar) Gamma globulin prepared from pooled mumps convalescent serum, and given in a dose of 20 ml. intramuscularly on the first day of the parotitis cut the incidence in another series to 8 per cent while the controls had 27 per cent (Gellis, *et al*). Gamma globulin from normal human plasma is of no value in mumps, having a very low mumps complement fixing antibody content

Treatment of the complications is largely symptomatic When orchitis is present, the patient should be kept flat in bed and the scrotum should be held elevated so that there will be no drag. Cold applications are usually found to be comforting, but ice bags should be removed one hour in each three When the swelling is marked and unusually distressing, puncture of the tunica vaginalis may bring relief of the tension, and thereby ease the pain and help to lessen the resulting atrophy Subcutaneous injections of stilbesterol have also been thought beneficial under these circumstances, the dosage to be given being 5 mgm each day, given intramuscularly ACTH and cortisone have also been used for treatment of orchitis The value of all these drugs has not yet been established. For the pancreatitis nothing should be given by mouth until the vomiting has ceased, and the bowels should be thoroughly opened with hot sodium bicarbonate enemas Sedatives given by hypodermic may be necessary. The first preparations to be retained by mouth will usually be starch liquids, such as a thin gruel or a fat-free broth thickened with rice or barley. Sweetened orange and other fruit juices and ginger ale also may be tolerated early. Cold or heat to the epigastrium occasionally proves helpful. In severe cases it may be found necessary to stop everything by

11

Chickenpox

Synonym.—Varicella.

Definition.—An acute highly contagious disease caused by a specific virus, and characterized by mild constitutional symptoms and by an eruption of papules and vesicles which develop in crops and dry up in a few days, leaving a granular scab

THE ETIOLOGY OF CHICKENPOX

Exciting Cause—The exciting organism is a virus occurring in the form of "elementary bodies" which are constantly found in great numbers in the vesicle fluid. They were obtained in pure suspension by Amies and are specifically agglutinated by the serum of patients convalescent from chickenpox By means of the electron microscope, the elementary bodies of chickenpox appear similar to those of herpes zoster, but can be differentiated from those of smallpox and of vaccinia which in turn are similar to each other The discovery of these elementary bodies has not yet contributed to the production of immune sera or prophylactic vaccines

The virus has been grown in tissue culture and specific antibody has been demonstrated in convalescent human serum by special technics

The infecting virus is present also in the blood early in the disease, and inasmuch as ruptured vesicles are a fairly common finding in the mouth in the first days of the disease, it can be presumed that the infecting virus also exists in a communicable form in the secretions of the nose and throat.

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Manner of Transmission.—The virus presumably enters the body through the mouth and nose.

There is considerable difference of opinion as to the contagious properties of this disease. Although some authors state that it is transmissible only by direct contact and very rarely by a third person, nevertheless it is probably that disease which most successfully defies isolation by medical aseptic technic. The infecting virus may be air-borne for a short distance, and it quite definitely can be carried by infected articles and by a third person. For instance, a boy, aged thirteen years, had chickenpox, and amused himself during his isolation by playing with a small loom for making bead necklaces On the completion of his case on December 24 the bead loom was put away in a cardboard box on a closet shelf On January 6 his two younger sisters, aged eleven and three years, found the box and played with the loom all afternoon. They had not previously been exposed to the brother's contagion, and a possible joint exposure elsewhere seemed impossible. Fourteen days later they both came down with chickenpox

Age, Race, Season, Sex.—Race, climate, season and sex have apparently no influence on the incidence of chickenpox. The disease is usually endemic in large cities, but may occur in epidemic form Because of its great infectivity the disease is usually contracted on the first exposure The vast majority of cases are, therefore, in young children but, many medical writers to the contrary, it is found occasionally in adults, especially those who have grown up in rural communities The disease has been reported present at birth and in the first days of life, also in a seventy-two-year-old woman

THE PATHOLOGY OF CHICKENPOX

The characteristic lesions consist of macules and papules many of which develop into vesicles and which occupy only the outer layer of the epithelium. Microscopic examination of the pocks shows first a swelling of the cytoplasm and of the

nuclei of epithelial cells. Typical balloon cells develop, some of which are multinucleated. Liquefaction of the swollen cells follows with the formation of vesicles, and intranuclear inclusion bodies have been observed in a number of cells within the vesicles. In smears prepared from vesicles, cells can be demonstrated undergoing amitotic nuclear division with the formation of multinucleate giant cells so characteristic as to be diagnostic of the presence of either chickenpox



FIG. 40.—Photomicrograph of an early skin lesion of chickenpox, showing the development of the bleb between the layers of the epithelium.

herpes zoster or herpes simplex. They are not found in other vesicular diseases.[1] The pocks of chickenpox may develop from several centers so that the fluid may be confined in several compartments or in only one. If multilocular, the partitions are said to radiate downward from the covering rather than upward from the central floor, as is described in smallpox. The red areola which often surrounds a pock for

[1] Blank, *et al.* J. A. M. A., **146**, 1410, 1951.

an area as large as 1 cm. in diameter is formed by distended capillaries and occasionally some infiltration. The fluid contained in the pock is at first a clear serous fluid, which later becomes cloudy and thicker as loose epithelial cells and some leukocytes accumulate in it When secondarily infected, the fluid becomes purulent

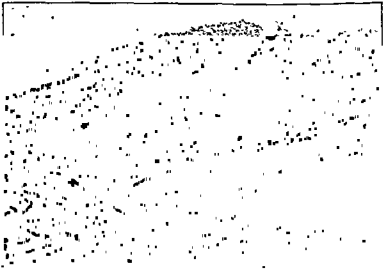


FIG 41 —Photomicrograph of an early mucous membrane lesion of chickenpox, showing beneath the epithelium lining the larynx a small area of necrosis surrounded by cellular infiltration

While there is still fluid in the pock the thin pellicle over it is unfortunately quite easily scratched off. As the fluid in the pock is absorbed, a scab forms which is somewhat granular in character and irregular in outline, and which adheres rather tightly. Later it becomes loose and quite easily detached. The vast majority of pocks are followed by rapid repair, with the skin returning to its normal condition. If, however, the scabs are scratched off too soon, or if secondary infection has taken place, the process extends deeper into the layers of the skin and involves the corium; as a result,

a shallow depressed scar is formed, which is at first reddish in color and somewhat pigmented, but which in two or three weeks becomes white and is liable to persist for many years

Pocks also occur on the mucous membranes causing lesions similar to those in the skin but slightly deeper in situation

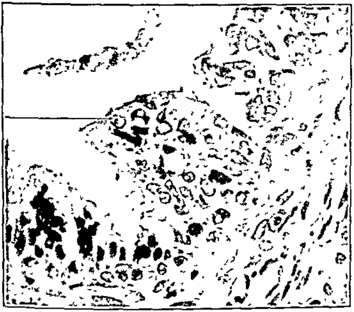


FIG 42 —High power (× 600) photomicrograph of intranuclear inclusion bodies in the bronchial epithelium of a case of congenital chickenpox The line points to one such inclusion body in a nucleus with a clear space around it and with the nuclear chromatin condensed at the periphery of the nucleus Other inclusion bodies are to be seen in other nuclei in the mucosa (From paper by E H Oppenheimer)

(Fig 41) and intranuclear inclusion bodies may be found in many cells in the mucosa (Fig 42) Occasionally at autopsy small spots of focal necrosis suggesting pocks are found in various organs such as the lungs, liver, and adrenals, and in the peritoneum. In extreme cases, especially in marantic

infants, actual gangrene of the skin may be found centering in pocks, particularly on the scrotum.

When death results from encephalitis complicating chickenpox, toxic degenerative changes in the nerve cells, perivascular loss of myelin in the white matter, and scattered hemorrhages in the cortex have been described.

Even in uncomplicated cases, there is customarily a slight leukocytosis.

IMMUNITY TO CHICKENPOX

There may be a short congenital immunity, because chickenpox is very unusual in the first two or three months of life, except when contracted before or at birth from the mother. *After the first few months every human being is apparently* very susceptible to this disease, and contracts it usually on the first exposure. When one child in a home has contracted the disease and not been isolated until the diagnosis has been made, the other susceptible children in the home may be expected to develop the disease in nearly 100 per cent of the cases. The disease occurs only in man, the lower animals having a complete natural immunity. Undoubted second attacks of chickenpox are extremely rare, but a few authentic instances have been reported.

INCUBATION PERIOD OF CHICKENPOX

The length *of time from exposure to the first appearance of* the eruption is usually fairly close to fourteen days, but it may be anywhere from ten to twenty days. Table 9 illustrates the duration of 127 incubation periods which began with fairly clear-cut exposures. All of these cases were personally seen, either in private practice or in a large private school Incubation periods due to exposure to a brother or sister seem to be a day or two shorter than those due to a schoolroom classmate.

TABLE 9.—INCUBATION PERIODS IN CHICKENPOX, SHOWING THE LENGTH OF THE INCUBATION PERIOD IN 127 SECONDARY CASES OF CHICKENPOX RESULTING FROM EXPOSURE AT HOME OR IN SCHOOL

Primary patients	Number of days									Average number of days
	10	11	12	13	14	15	16	17	18	
Relatives	2	5	12	7	14	3	3	1	1	13.21
Classmates		1	4	10	17	22	13	10	2	14.82
Total	2	6	16	17	31	25	16	11	3	14.21

TABLE 10.—INCUBATION PERIODS IN CHICKENPOX, SHOWING FIVE ILLUSTRATIVE EXPOSURES

Primary patients	Number of days								
	10	11	12	13	14	15	16	17	18
Gordon H.					3	4	1	1	
James R		1*	1*	1*	3	5	1	1	
Dorothy R		1	2	1					
Charles K					4				
Betty D					3*		1		

* Family cases; the others are classmates

THE CLINICAL MANIFESTATIONS OF CHICKENPOX

During the period of incubation there are usually no evidences of ill health, nor is the patient ordinarily able to transmit the disease until perhaps the last half-day. The period of invasion is usually absent in young children, but in older children and in adults there is commonly a period of twenty-four to thirty-six hours before the appearance of the exanthem, during which the patient is apt to have a considerable amount of headache, malaise, anorexia, and perhaps fever up to 101° or 102° F. With these symptoms there may

be also a slight prodromal eruption, scarlatiniform or macular in type, lasting perhaps twenty-four hours.

The fastigium of the disease, or period of *the exanthem*, is usually very sudden in onset. The skin of a small child may be entirely clear at 9 A M, and yet at 11 A.M. show 5 or 6 small macules, or even 1 or 2 vesicles, and at 3 P.M. show 10 to 20 lesions with small vesicles and perhaps 1 or 2 scabs Occa-

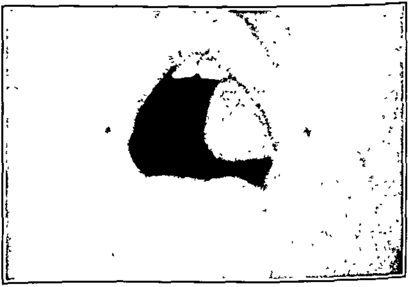


Fig 43 —Chickenpox Showing a lesion on the hard palate, and three on the upper lip.

sionally twelve to twenty-four hours before lesions are found in the epidermis, they may be found on the mucous membrane of the soft palate or inside the cheek and in isolated instances a single papule or two may appear in the skin two or three days before the generalized exanthem. For two to four days the pocks appear in crops, and may eventually total as many as 1000 or more, or be no more than 5 in number altogether. A characteristic feature of chickenpox

PLATE VII



Chickenpox
Showing early lesions slightly magnified
(From the collection of H A Towsley, M.D)



Chickenpox.
Showing an early but extensive eruption on the chest.
(From the collection of L H Koplik, M D)

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therefore, is that all stages and sizes of the lesions may be found present at the same time and in the same vicinity.

Location.—The lesions usually appear first on the skin of the body, and in the scalp where they are frequently discovered as small lumps against which a comb strikes. The successive crops involve the head and body particularly, but a number of lesions may appear also on the extremities, and even a scattered pock or two in the palms of the hands and the soles of the feet. In general, however, chickenpox may be considered centripetal in character, while smallpox, which particularly involves the face and the extremities, is centrifugal. The lesions may involve the various mucous membranes, such as the mouth, where they appear oftenest on the soft palate, and usually as small crater-like ulcers surrounded by a small areola of inflammation. Lesions are also occasionally situated on the inner surface of the eyelids, where they cause considerable swelling and discomfort. In women the mucous membrane of the vulva may be involved, causing a very considerable distress from itching, and possibly painful urination if the urethral orifice is involved.

Appearance.—The average pock appears first as a small red macule, 2 or 3 mm. in diameter, which in the course of a few hours becomes a papule. It then develops at its top a small drop of clear fluid, covered over by a thin pellicle of skin. This pellicle is usually rounded, but may show a central depression or umbilication if the pock is multilocular. The fluid in the pock soon becomes slightly turbid, and the pellicle becomes thicker and changes into a dry, brown scab. Until the individual lesions have reached this stage they usually itch considerably, causing what is often the only uncomfortable feature of the disease. To the touch the lesions of chickenpox all seem small and superficial and without induration, in contrast to the lesions of smallpox, which are harder and more deeply seated in the skin. Many of the pocks may be surrounded by an irregularly shaped red areola of congestion, but this may be entirely lacking, and occasionally one finds a pock which looks like a small drop

of dew on the normal skin. The top of the pock is at first readily scratched off, but as the underlying pock heals and becomes dry, the scab becomes temporarily more tightly adherent It later loosens and is cast off, leaving a small, slightly pigmented crater-like surface, which ordinarily

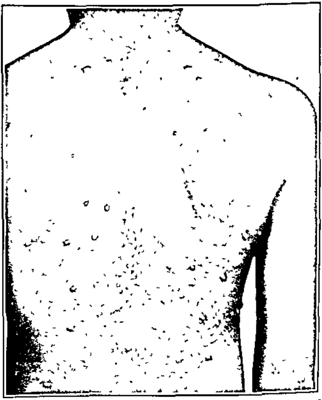


FIG. 44 —Showing the early lesions of chickenpox in a young colored girl (From the collection of A. Benson Cannon)

clears up and disappears In some cases a large proportion of the macules do not go on to vesicle formation, but fade and disappear without further destruction of the tissue. On the other hand, where the scab has been scratched off too early and a secondary infection has ensued, the pock

may be followed by scar formation which may be evident for years. The rash of chickenpox does not become confluent, as may be the case in severe smallpox, but inasmuch as viruses tend to localize in irritated tissues, scratching the skin early in the disease will cause a marked increase in the number of lesions in that scratched area. In areas of preexisting skin inflammation the lesions as in smallpox may be especially numerous or almost confluent.

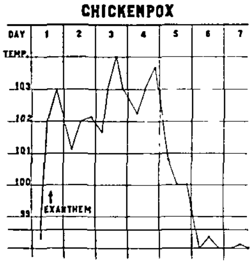


FIG. 45.—An unusually severe case of chickenpox in a boy, aged four years. On the day of onset he played outdoors in the morning, felt sick at noon and showed the first macules at 3 P.M.

There may be no fever at any time, but it is usual for the temperature to rise the day of the onset of the eruption to perhaps 101° F., returning to normal in twenty-four to forty-eight hours. In severe cases, however, even though uncomplicated, it may rise to 104° F. or more and persist for several days. This is particularly true of adults who also are apt to experience a great deal of malaise and prostration.

Fig. 43 shows the fever curve in a case of chickenpox which attacked a boy, aged four years, about a week after he had been released from isolation after a combination of illnesses, which included scarlet fever, measles, bronchopneumonia, and otitis media. (Fig 23, page 188.) Incidentally, his infection was unquestionably carried to him by a third person, because except for the last three days he had not been out of his home for over seven weeks, and there were no other cases of chickenpox in the building

The active course of chickenpox is usually entirely over in seven to ten days After the onset of the eruption new lesions appear for three or four days, but by the end of seven to nine days most of the pocks have dried up and are covered by hard, brown scabs. During the next two to four days these scabs appear to contract and become loosened from the underlying tissue so that they are easily rubbed off Two weeks from the onset of the disease few if any scabs may be present, although an occasional scab may be found caught in the scalp The several white flat scars which may survive are slightly indented, and more superficial and regular than smallpox scars

THE COMPLICATIONS OF CHICKENPOX

The vast majority of cases of chickenpox follow their normal course without complication Occasionally a child will infect a pock by scratching, and a superficial staphylococcus infection may develop. In one young girl, aged sixteen years, 33 small boils, pimples, or infected pocks required surgical treatment Impetigo may also develop. In either case these infections of chickenpox lesions are apt to be followed by scarring. Such other pyogenic conditions as otitis media, suppurative lymphadenitis, cellulitis, and erysipelas have been reported especially in institutional cases. Gangrene of the skin at and around the site of large pocks may take place in severe cases of chickenpox, particularly in marantic infants or those debilitated by any

wasting disease, and fatal cases have been reported where this complication has occurred Chickenpox has also proved fatal in at least three children with asthma who were being treated with cortisone

Encephalitis in rare instances may be observed similar to that following vaccination, smallpox, and measles, with very variable onset and course Almost every sign indicative of central nervous system involvement, such as neck stiffness, fever, excitement and convulsions, or apathy and stupor, may be encountered Ataxia is somewhat more common than in measles encephalitis The prognosis has not been too bad, in one series only 5 per cent dying, and 80 per cent recovering with no detectable abnormalities

The presence of chickenpox as a complication of other contagious diseases is in no way uncommon, since chickenpox is perhaps the cross-infection most difficult to prevent in a contagious disease hospital

THE DIFFERENTIAL DIAGNOSIS OF CHICKENPOX

1 *Smallpox* —*Typical cases of smallpox are usually very* easily distinguished from typical cases of chickenpox, but mild smallpox or severe chickenpox may so resemble the other disease as to be very confusing In fact, it has been customary for the New York City Department of Health to send a diagnostician to verify the diagnosis of each reported case of chickenpox in an adult

In smallpox there are usually very definite prodromal symptoms, beginning with chills and considerable fever, severe aching pains in the head and back, nausea and vomiting, and marked general malaise, all of which last for two or three days—the severity varying with the ensuing eruption. These symptoms then abate, to be followed during the ensuing development of the skin lesions by a secondary rise in temperature, which lasts a week or more until the pocks have begun to dry. In contrast to the above, prodromal symptoms in chickenpox rarely appear in children In older

children and adults there may be headache, malaise, and moderate anorexia, and perhaps fever to 101° or 102° F., but there is usually no vomiting, and these symptoms last only twenty-four to thirty-six hours. In isolated instances they may be as marked as the prodromal symptoms of mild cases of smallpox. There is no secondary rise of temperature in uncomplicated chickenpox

Following a sharp lessening of the constitutional symptoms, the eruption in smallpox begins to appear on the third or fourth day, with the following characteristics: (1) Each lesion develops from the onset of symptoms to the vesicle stage in about six days, and from the onset to the scab stage in ten to twelve days, except in modified cases, where the course may be shortened to perhaps six days; (2) in a given area the lesions are similar in size, shape and development, but lesions found on the extremities may be slightly younger *than those found on the face*; (3) *the lesions are multilocular*, often umbilicated and fairly circular in outline; (4) the eruption involves particularly the face and the distal part of the extremities, especially the exposed or extensor surfaces, *i e*, the location of the lesions is centrifugal, (5) the lesions are set deep in the skin and are palpable as hard, shot-like lumps, (6) in severe cases the eruption may become confluent In contrast to this, the eruption in chickenpox begins in the first twenty-four hours, with the following characteristics (1) Each lesion develops from the onset to the vesical stage in only a few hours, and to the scab stage in from one to three days, (2) the lesions vary greatly in size, and since they appear in successive crops, may be seen simultaneously in the various stages of development, (3) the lesions that are multilocular and umbilicated are the exception rather than the rule, and most of the lesions are quite irregular in outline; (4) the lesions are centripetal, involving the upper part *of the arms and legs more than the distal* parts, and the body more than the extremities. A few chickenpox lesions may be found in the palms of the hands and the soles of the feet in marked cases, but the presence of numer-

ous hard, brownish crusts imbedded in the skin of these areas is usually indicative of smallpox, (5) the lesions are more shallow than in smallpox; (6) the eruption does not become confluent except in patients with preexisting skin inflammations such as infantile eczema.

In patients who have been vaccinated at some rather distant time, immunity to smallpox may be only partial, and a modified type of that disease may occur in which the prodromal symptoms are very mild and the eruption sparse, early to begin, and rather quick to run its course. These cases offer special difficulty in their similarity to chickenpox. The presence of a recent vaccination scar, however, is of great help in ruling out the presence of smallpox Since second attacks of the two diseases are extremely rare, a history of a previous attack of one or the other disease is also of value in the differential diagnosis The examination of stained smears *prepared from the vesicles may enable a definite differentiation* (See pages 337 and 352)

2. *Herpes Zoster.*—The lesions of herpes zoster and chickenpox may resemble each other quite closely, but usually the lesions in herpes zoster are larger and much more apt to become confluent and form bullæ, and there is much more of an erythematous base The vesicles of herpes zoster are grouped along the line of the affected nerve or nerves, whereas chickenpox has a generalized eruption Pain is nearly always a marked symptom in cases of herpes zoster, but does not occur in chickenpox The former is rare in childhood, and the latter unusual in adults.

That there is a possible etiological relationship between herpes zoster and chickenpox has been discussed in medical literature for a number of years. Cases of herpes zoster have seemed to be the cause of chickenpox, and there have been instances of apparent cross-protection For instance, an eight-year-old girl who had been in school the first four days after the holidays was then diagnosed as having a typical painful herpes zoster with confluent blebs over the right sixth rib anteriorly Fourteen days later four class-

mates developed typical chickenpox, a fifth the following day, and a sixth the seventeenth day. No other possible exposure *could be found. Seven susceptibles escaped infection.*

By the electron microscope the viruses of chickenpox and of herpes zoster appear similar and complement-fixation tests using vesicle fluids seem to indicate a close relationship and possible identity of the two viruses Simultaneous cases of chickenpox and herpes zoster which have been reported suggest that some strains of the varicella virus may have a neurotropic tendency and can be responsible for both types of infection On the other hand, there is the possibility that the viruses of the two diseases may be distinct entities, but may possess certain antigenic and disease-producing constituents in common The matter must still be regarded as unsettled

3 *Rickettsial Pox*[1]—This is a domiciliary disease entity which was identified in 1946 in Brooklyn by the staff of the Bureau of Preventative Diseases of The New York City Department of Health It is caused by infection with Rickettsia akari and is transmitted to house mice and man by the bite of the blood-sucking mite, *Allodermanyssus sanguineus.* This tiny mite when empty of blood is about 1 mm in diameter and colorless, but when engorged with blood is red and much larger Its host in nature is the house mouse and it is also found on the walls of dirty cellars where garbage and other food for mice are allowed to accumulate.

Since 1946 from 50 to 150 cases a year have been reported in greater New York City, and recently 8 cases in one small apartment house in Hartford, Connecticut, and 4 in Philadelphia.

The clinical manifestations of the disease have three features. (1) The primary lesion at the site of the insect bite: At first a firm red papule, it grows to 1 to 1½ cm in diameter. A vesicle forms in the center, then shrinks and dries forming a black scab which after about three weeks falls off leaving a small scar. The lesion is not tender and does

[1] Reprinted from Jour Pediatrics, Philip M Stimson

not itch The regional lymph nodes normally become enlarged but are only slightly if at all tender.

(2) The constitutional manifestation: About four to seven days after the bite, the patient suddenly develops considerable fever, chills and sweats, headache, backache, malaise, and often photophobia These various manifestations persist about a week and gradually clear up.

(3) The rash An eruption appears one to four days after the onset of the fever It is usually generalized in distribution without a pattern, except that, like chickenpox, it is unusual on the palms and soles, and again like chickenpox, lesions have been seen on the tongue and palate. The pocks are discrete, begin as maculopapules, develop vesicles on top which dry and form small scabs which in turn fall off and leave no scar The course of the pox is four to seven days in duration, and there are no subjective symptoms due to the eruptions There is usually a moderate leukopenia There have been no complications and no deaths There is no specific treatment indicated but aureomycin, terramycin and chloramphenicol apparently are beneficial

Severe chickenpox in the adult may closely resemble rickettsial pox, both diseases having prolonged and distressing eruptions, except that while in chickenpox the vesicle replaces the papule, in rickettsial pox the papular element of the lesions remains throughout, the vesicles surmounting the papules The primary lesion of rickettsial pox should be looked for and complement fixation tests can prove this latter diagnosis A history of exposure to chickenpox is of course important, or on the other hand, the recognized presence of house mice and of unsanitary conditions can be significant.

The "Weil-Felix" reaction with Bacillus Proteus OX19 which is positive in such other rickettsial diseases as typhus fever, both epidemic and endemic, and in Rocky Mountain spotted fever (neither of which have vesicular lesions) is negative in rickettsial pox

4 *Impetigo Contagiosa.*—This disease is characterized by the formation of vesicles which rapidly become pustular, form

crusts, and become irregularly confluent. The lesions are usually found only in areas that are easily scratched, notably around the nose and mouth. In the majority of cases the face only is involved. As a result of scratching or rubbing, lesions increase and spread irregularly, but do not appear in crops as do chickenpox, nor are they scattered over the body In impetigo there are no constitutional symptoms except in very severe cases, and the course of the lesions is apt to be much slower than is that of the pocks of varicella.

5 *Syphilis* —In the papular and pustular stage of syphilis the skin lesions may bear some resemblance to those of chickenpox, but the course is markedly different, and the primary sore may still be demonstrable Clear vesicles preceded by small papules are not found.

6 *Pemphigus* —This is a serious disease which occurs particularly in infants and may be confused with the gangrenous type of chickenpox. The eruption is characterized by bullæ, which vary in size from a few millimeters to several centimeters in diameter, and appear to rise from the surface of the skin without a surrounding erythema. The disease is usually accompanied by a considerable elevation of temperature

7. *Insect Bites* —The results of insect bites are usually found only on exposed areas of skin, rarely in the scalp, and never in the mouth The lesions of scabies also are not found on mucous membranes and are most usual on areas reached by fingers.

8 *Various other Skin Diseases* —Various other skin diseases, such as dermatitis herpetiformis, acne, Kaposi's varicelliform eruption, and certain forms of eczema, have occasionally been confused with chickenpox, as also have the eruptions caused by certain drugs, such as bromides and the sulfonamides.

THE PROGNOSIS OF CHICKENPOX

It may be safely stated that uncomplicated chickenpox is never fatal, but in the rare instances when it is complicated

by gangrene, or by severe secondary infections, it may cause loss of life in debilitated patients. In the average case a prompt recovery within two weeks may be safely predicted, with very little if any scarring, but warning should be given that if the pocks are allowed to become infected or if the scabs are scratched off before the pocks are completely healed, small white scars may persist for years.

PERIOD OF INFECTIVITY OF CHICKENPOX

On the evidence now available, this period should be considered as lasting from about twenty-four hours before the appearance of the eruption until about seven days after its appearance. At least one authority has stated that a chickenpox patient can transmit the disease as long as four days before the rash appears, but this must be unusual. It is certainly possible for the disease to be transferred from a patient several hours before the appearance of the exanthem. Although it has not yet been determined how long a patient remains able to infect others, the current opinion is that the danger is over when there are no longer any actual vesicles, *i e*, that the disease is not spread by the dry scabs *per se*. The patient may remain contagious for several days longer, however, unless a thorough bath and shampoo have been taken.

ISOLATION AND QUARANTINE FOR CHICKENPOX

In most communities chickenpox patients are neither isolated nor placarded, but are excluded from school until most of the primary scabs have disappeared. A safe rule is: After an attack of this disease pupils may return to school forty-eight hours after the rash has lost its vesicular appearance and become crusted provided that there has been a thorough bath and shampoo.

Chickenpox, being extremely contagious, is very difficult to control in hospitals, orphan asylums, and boarding schools

without drastic isolation and quarantine. The strictest medical aseptic technic in a hospital ward often does not seem sufficient to prevent the spread of chickenpox from one cubicle to another Accordingly, distance and fresh air should be added to the barriers that aseptic technic ordinarily erects between patients with communicable diseases Chickenpox patients should, therefore, be in a separate building and there should be no means of contact communication between them and the other children

For handling chickenpox exposures in day schools, the following rules may apply especially if it seems essential to minimize the spread of the disease:

A child is considered exposed if he has been in contact with a patient during the twenty-four hours preceding the rash, or during the disease including the period of vesicles, a total of about a week

School children who have been exposed at home and who have not had the disease may return to school after the third day following the appearance of the patient's rash, provided the patient is properly isolated They should then be excluded from the twelfth day after the first exposure until the sixteenth day after the last exposure The first part of this regulation is to protect an otherwise unexposed school from a child who after a common original exposure may be a day or two slower than the patient in developing the disease. And since, in family exposures, nearly 100 per cent of children contract the disease, exclusion from school at a time when the child is liable to have the onset of his attack is not only justified but necessary to prevent the introduction of this disease into the school.

Children exposed at school or elsewhere than at home, who have not had this disease, may continue at school if carefully examined at home before leaving for school and if examined at school once or twice during school hours each day, from the eleventh through the nineteenth days after the exposure. If at these examinations any evidence of ill health is found, such as fever, headache, or malaise, or if any new spot of

any kind is discovered in the skin, the child should be immediately excluded from school. By such a system chickenpox can, in most instances, be kept from spreading too markedly, and at the same time the children may be spared the loss of time from school.

Exposed children who have had the disease may continue at school, provided there is no further close exposure to the disease

PROPHYLAXIS IN CHICKENPOX

With chickenpox there is ordinarily no great necessity for such protective measures as inoculations because of the usual mildness of this disease itself, but in institutions, particularly where there are numbers of infants in poor physical condition, protective inoculations may be found desirable Using the lymph found in early pocks, various investigators have tried preventive vaccination in a manner similar to vaccination against smallpox Conflicting reports of results have been made. Some have obtained so-called "takes" and protection against the disease in a large proportion of the cases; others have not been so successful. There apparently has been no mention whether persons vaccinated in this manner have been able to infect others

Gamma globulin has no appreciable prophylactic effect in chickenpox.

Under ordinary circumstances in a family, by the time the first case has been diagnosed, the rest of the children have been thoroughly exposed and almost unquestionably infected It is, therefore, usually hardly worth while to separate them rigidly from the patient They may all be confidently expected to show evidences of the disease about thirteen days from the onset of the patient's eruption.

THE TREATMENT OF CHICKENPOX

There is no specific remedy for the treatment of chickenpox

The patient should be kept in bed during the presence of any elevation of temperature and twenty-four hours more

Throughout the contagious period he should be isolated from non-exposed susceptible children, though not necessarily kept indoors. The utmost pains should be taken to prevent secondary infection of the pocks, as by the patient's scratching. Accordingly the finger-nails should be kept scrupulously clean and trimmed very short. Where itching is marked and scratching uncontrollable, white wash gloves may be kept on the patient's hands, or it may be necessary to splint the elbows or use aluminum mits. The itching may be relieved by applications of calamine and zinc lotion, or by various soothing ointments. A homeopathic ointment containing obtundia and calendula has been found notably successful in controlling this itching, particularly of the genitalia. Daily cleansing sponge or tub baths should be given, but with *great caution, care being taken not to rub the scabs off the pocks.* Keeping the pocks greased also helps to keep the scabs adherent.

Otherwise the treatment is entirely symptomatic. Infected lesions have been treated with antibiotic ointments with good results. The more severe complicating infections will require antibiotic treatment.

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12

Smallpox

Synonyms.—Variola, Varioloid (attenuated cases), Alastrim (a mild form). The word *small* was introduced in the sixteenth century to distinguish this disease from the Great Pox, or syphilis.

Definition.—An acute, highly contagious disease, characterized by an initial period of about three days of fever, headache, and backache, followed by a generalized eruption which passes through stages of papule, vesicle, pustule, and crust, with renewed constitutional manifestations at the time of pustulation, and with a tendency to secondary infection with a streptococcus.

The disease has been a scourge of all countries for many hundreds of years, but has prevailed particularly in India (250,000 cases in 1933) and in Africa. As recently as 1875 there were 1899 deaths from smallpox in New York City alone, and 410 in 1901. In the years 1933 to 1945 there was only 1 case in that city, but in 1947 there were 11 infections that resulted from a case that came in from Mexico. Seven of the western states actually prohibit compulsory vaccination. However, in the two years 1952 and 1953 there has been a total of only 34 cases in the whole United States.

The prevalence of smallpox in a community is a measure by which the efficacy of its health regulations may be judged, particularly the diligence in the application of the preventive measure of vaccination.

THE ETIOLOGY OF SMALLPOX

Exciting Cause.—Smallpox is reproduced experimentally only with difficulty. The most suitable animal is the monkey

in which cutaneous inoculation produces a definite local lesion with moderate constitutional changes The inoculation of lower animals, such as the rabbit, produces only slight local inflammatory lesions with but little general reaction. However, material collected from inoculated monkeys is more effective in producing lesions in the lower animals, the virus becoming definitely modified by animal passage and identical with the virus of vaccinia, being very readily transmitted to laboratory animals by skin inoculation The vaccinia virus has been extensively studied and facts pertaining to it presumably apply also to the virus of smallpox.

Paschen, 1906, demonstrated in the vesicular fluid of vaccinal pocks small coccal bodies which have been termed elementary or Paschen bodies, and which have subsequently been found in calf lymph and tissue culture preparations, and still more recently in the vesicle fluid from the lesions of smallpox. The fluid part of vaccinal lymph which remained after the removal of the elementary bodies by ultracentrifugation was inactive These elementary bodies have been extensively studied, particularly in England, and are considered to represent the actual virus (Fairbrother)

As seen with an electron microscope, these elementary bodies of the smallpox virus are quadrangular with rounded edges, from 200 to 250 millimicrons in diameter and are usually not grouped but separate The elementary bodies of chickenpox are smaller and variable in size, ranging from 150 to 200 millimicrons in diameter They are apt to be spherical in appearance and to appear in groups, and are in general, quite easily distinguishable from the elementary bodies of smallpox

The virus is comparatively resistant to glycerin, phenol, ether, and low temperature In fact, glycerin is used in the preparation of vaccine virus for dilution and for the destruction of contaminating organisms, and for preservation the virus must be kept as close to a freezing temperature as possible. It is destroyed by potassium permanganate and

by heat over 55° C. It can readily be cultivated in tissue cultures.

Suspensions of vaccinia virus give various specific reactions in the presence of such a specific immune serum as that of convalescent or immunized patients or of rabbits after inoculation. Precipitin and agglutination reactions with the elementary bodies have been reported, and Parker and Muckenfuss have demonstrated by the technic of complement fixation a specific reaction between the virus contained in the pock fluids both of vaccinia and of smallpox and an immune serum obtained from an inoculated rabbit.

Mode of Infection and Infectivity.—The infecting agent is present in the skin in all the stages of the pocks, and in the lesions of the mucous membranes, and also in the blood stream where the virus can be isolated during the early stages of the disease but not after the second day of fever, except in cases which are to prove fatal. The infection can be transmitted from the mother to the fetus *in utero*, usually about the time of the onset of the clinical illness in the mother. Epidemic evidence suggests to English authors that most cases of smallpox are not contagious until about the time of appearance of the skin eruption,[1] but they certainly are markedly so during all stages of the actual eruption, until all crusts have disappeared. The bodies of those who have died of the disease even before the development of the eruption are highly contagious. No animal is known to be susceptible to the disease but contagion may be carried by healthy carriers, either man or beast, by clothing and other contaminated objects, and by air-borne particles of moisture from the body secretions or of moist or dried scabs. The virus can survive in dust for ten days and in dry scabs kept in a bottle for a year. The distance by which the disease can be air-borne has seemed to be many yards in the direction of the prevailing wind, but most authorities believe that the air-borne spread

[1] Brit. Med. Bull., 9, No. 3, 191, 1953

of the disease over distances greater than a few yards is unlikely.

The virus enters the body by the upper respiratory tract and is apparently absorbed from the mucous membrane without producing a local lesion No symptoms or signs are evident during the growth of the virus and the accompanying production of toxin in the organism, until there has been sufficient development at the end of about twelve days to cause the onset of the clinical manifestations.

The disease can also be contracted by inoculations of the skin, as well as of the mucous membranes, but probably not through the intact skin

Season, Sex, Race, and Age.—In temperate climates, smallpox is rather more common during the cold-weather months, but in tropical countries the malady is said to be worst in the hot months, dryness presumably favoring its spread Both sexes are equally susceptible All nations and peoples have been attacked by the disease, but the colored race appears even more susceptible than is the white No age is immune, and infants are particularly susceptible, both before and after birth Before the practice of vaccination became general, the disease was essentially one of early childhood, practically all adults having been attacked long before adult life. In unvaccinated populations five-sixths of the smallpox deaths were in children under six. In recent years, because of the general protection of children from the disease, it is more commonly seen in adults whose protection from childhood immunization has diminished The disease is especially apt to be spread by migratory laborers, seamen, and vagrants

In the different countries in recent years, strains of smallpox are of different degrees of virulence but breed true even over a long series of years In India and the Far East, northern Africa and Mexico, the prevailing strains are virulent, producing true smallpox, while in England, Canada, the United States, the West Indies and South Africa, the usual strains are non-virulent and produce alastrim.

THE PATHOLOGY OF SMALLPOX

The virus of smallpox apparently produces a toxin which gives rise to the constitutional symptoms and fever, especially of the invasive stage, but which also has a vasomotor and angiolytic effect evidenced by the initial petechial rashes and by the hemorrhagic forms of the disease. The entry of the virus into the blood steam must follow closely on the toxic invasion (Blaxall) Certainly vaccinia virus after inoculation by any route has a tendency to become widely distributed in any tissue of the body and has been found in the blood of children several days after ordinary vaccination.

According to Unna, in the papulo-vesicular stage the prickle cells in the upper portion of the epidermis become edematous, develop vacuoles and undergo fibrinoid degeneration with formation of a vesicle. In the lower portion of the prickle cell layer the epithelial cells separate and round up in large "balloons" containing 1 or 2 nuclei. Vertical columns of relatively intact epithelial cells remain in the vesicle making it multilocular; as the vesicle enlarges, the upper parts of the trabeculæ spread in a fan-like fashion. In the derma (or corium) the blood vessels are surrounded with plasma cells On the fifth day the blood vessels dilate, polymorphonuclears appear around them and in their lumen and the emigration of leukocytes into the vesicle begins, converting the vesicle into a pustule. The margin of the pock becomes more elevated and the pock assumes an umbilicated appearance. If the horny layer remains intact, the pustule dries up, the basal layer remains intact and no scar remains. If the surface layer breaks down, secondary infection with streptococci and other bacteria occurs with formation of a large amount of pus and a copious foul smelling discharge; the basal layer of the epithelium becomes destroyed, and, after the scab is cast off, a permanent pitted scar remains

In

bodie

and vaccinia Their presence constitutes an important diagnostic feature.

Lesions of the mucous membranes are somewhat proportional to the extent and severity of those of the skin, and analogous in structure, and those mucous membranes to which air has free access are especially involved, particularly the mouth and pharynx. The bladder and urethra are not involved except the urethral orifice A fibrinous or seropurulent pleurisy is a not uncommon finding at autopsy,



FIG 46.—The vesicle of smallpox (drawing of cross-section magnified 30 times) To the right is a young multilocular vesicle formed by reticular degeneration with balloon cells on its edges To the left, a multilocular vesicle of more advanced stage shows reticular degeneration above while below are only occasional balloon cells The comparative absence of inflammatory reaction in the cutis is to be noted (McCarthy, Histopathology of Skin Diseases, courtesy of C V. Mosby Company)

as are also small patches of lobular pneumonia The liver shows cloudy swelling and toxic degeneration, and the spleen is enlarged General lymph node enlargement is present in the pustular stage, and the kidneys show varying degrees of interstitial infiltration and tubular degeneration The serous membranes show congestion and small ecchymoses, but in the hemorrhagic cases extensive hemorrhagic conditions may be found in almost any part of the body.

Blood in Smallpox.—In smallpox at first there is ordinarily no increase in the total number of leukocytes but rather a relative increase largely of mononuclear cells and to a lesser extent of eosinophils, which may comprise 3 to 10 per cent of the total number during the first three weeks of the disease, and even more during convalescence. Myelocytes may be present in considerable numbers. During the pustular stage the leukocytes increase markedly, particularly if there is a secondary infection A secondary anemia is apt to develop rapidly during the course of the disease.

THE CLINICAL MANIFESTATIONS OF SMALLPOX

Incubation Period.—The duration of the incubation period is usually about eleven or twelve days, with ordinary limits of eight to fourteen days. Exceptional instances of shorter or longer periods have been reported. Smallpox resulting from cutaneous inoculation develops in six to eight days, because of the different portal of entry Varioloid and alastrim are slower to develop, often taking fifteen or more days

The incubation period is ordinarily unaccompanied by any manifestations of ill-health, but an occasional case may show loss of appetite, headache, and general malaise towards the end of the period.

The Period of Invasion, or Initial Stage of Toxemia.—The onset of smallpox is usually sudden and severe, and characterized by a chill in adults, or by vomiting or convulsions in children Fever develops at once, reaching 102° to 104° F. or more, within twenty-four hours, and the increase in pulse- and respiration-rates is ordinarily proportionate to the elevation of the temperature While headache is a conspicuous symptom and often distressing, pains in the lower half of the back are especially common and of some diagnostic significance. Nausea and vomiting are frequently present, and constipation is the rule. Dizziness and general malaise are common features and prostration is usually marked.

In general, the patient rapidly becomes very distressingly miserable and occasionally very seriously ill.

In many cases the manifestations of this initial stage are much less severe than those described and lead to very mild forms of the disease. While the more severe invasions usually are followed by unmitigated manifestations of the eruptive period, this is not necessarily invariable. After three or four days the initial prostration and malaise diminish and the temperature returns approximately to normal The other manifestations clear up markedly, and the patient feels greatly improved and enjoys a temporary respite from the distress and prostration of the disease

Prodromal Rash.—In a small proportion of the cases a prodromal rash may appear within twenty-four hours of the onset of symptoms. Occasionally the eruption is morbilliform or erythematous, is found particularly on the body, and lasts only about twenty-four hours In other cases the eruption is hemorrhagic in type, is characterized by petechiæ or even purpura, and is most commonly found on the lower half of the body. This hemorrhagic type of eruption is apt to persist into the next stage of the disease and is especially frequent in the hemorrhagic forms of smallpox

Period of Eruption.—Usually about the end of the third day of the illness, the exanthem appears in the skin, particularly on the forehead and temples and occasionally also around the wrists. It spreads rapidly to the rest of the head, and to the forearms and hands, and then in succession to the back, arms, breasts, and, finally, legs and feet, taking perhaps two or three days to complete its distribution On any given small area all the lesions appear at approximately the same time.

In general, the lesions are most marked on the head and beyond the elbows and knees, that is, they are centrifugal in distribution. (See Fig 49, page 349) There are more pocks on the shoulders and chest than lower on the trunk, and more on the extensor surfaces than on the flexor. They are usually especially numerous or even confluent at any area

of irritation or previous inflammation of the skin. No matter how sparse the rash, the eruption never misses the face.

The eruption begins as small red macules which almost at once become elevated, darker in color, and firmer, so that the resulting papules seem imbedded in the skin. By the fifth or sixth day of the disease, fluid has appeared in most of the earlier lesions, and an irregular red areola may surround each vesicle. At this stage the lesions have the shape, size, and feel of a split pea in the skin. The vesicle is extremely firm and presently develops a glistening, pearly

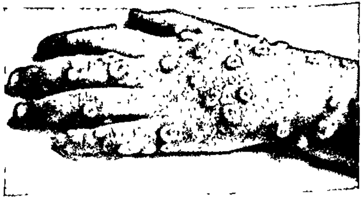


FIG. 47.—The eruption of smallpox Large umbilicated pustules found on the seventh day of a smallpox eruption. (Schamberg and Kolmer, Acute Infectious Diseases)

appearance. A characteristic feature of the early lesions is umbilication, shown by a depression in the center of the pock, probably representing a hair follicle or the duct of a sweat gland. By the ninth day of the disease (the sixth or seventh of the eruption), the contents of the pocks become turbid and later purulent. The lesions become even larger than before and many appear definitely multilocular.

During this period of development of the rash there is a gradual return of the fever and malaise, reaching its maximum about the time of pustulation, the degree varying with

PLATE VIII



Smallpox.
Showing the exanthem on the face Note eyelids and nostrils.
(From the collection of H A. Towsley, M D)



Smallpox
Showing pocks four or five days old on a forearm.
(From the collection of H A Towsley, M D)

the number and severity of the lesions Restlessness, insomnia, even delirium may develop Pain is customarily very distressing in the head, back, and extremities, particularly at the site of the most extensive eruption, and there is also a marked burning sensation of the affected skin

The eruption also develops on the mucous membranes, occasionally starting a few hours before the exanthem. It involves particularly the mucous membranes of the pharynx, but may appear also in the larynx, cheek, and nose, on the tongue, on the palpebral conjunctiva, on the external genitalia, and in the vagina, with corresponding manifestations of pain and swelling in the affected areas. The eyes are frequently swollen shut. The voice becomes hoarse, and there is marked difficulty in swallowing.

About the tenth day of the disease (the sixth or seventh day of the eruption), the contents of the pocks become purulent, those on the face being affected before those on the body and lower extremities The individual pustules become large and stand out conspicuously from the skin. The underlying tissues, particularly of the face, become swollen and puffy After two or three days the lesions begin to dry and present a shrunken appearance with a somewhat more yellow color, and severe itching is apt to replace the former actual pain and burning in the skin Many of the pustules rupture, the sticky yellowish pus drying in the form of crusts on the skin and causing a very foul and troublesome odor Discrete lesions develop brownish scabs, granular in structure, which become dry and eventually are cast off, leaving pitted marks, particularly on the face. Secondary infections of the pocks and particularly of the lesions of the mucous membranes are common, and general sepsis may develop A general erythematous eruption, toxic in origin, may be present for two or three days during this period

With the drainage of the pustules and the gradual improvement, the temperature begins to fall, and the general consitutional manifestations become less marked. Some cases,

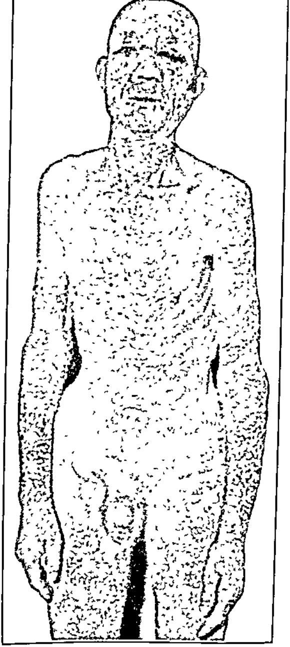


FIG 48 —Patient with pustular eruption of smallpox (Rivers, Viral and Rickettsial Infections of Man, courtesy of J B Lippincott Company, and the National Foundation for Infantile Paralysis, Inc)

however, will have had surprisingly little fever or constitutional disturbance considering the extent of cutaneous involvement The drying of the lesions has usually begun by the eleventh or the twelfth day of the eruption, earlier in the mild cases which may be quite clear in three weeks, but in the more severe cases three weeks or more are usually necessary just for the shedding of the crusts, making the entire duration of the disease five or six weeks. The scabs of the palms of the hands and the soles of the feet are apt to adhere longest, being imbedded in the thick layers of the skin.

When the deeper layers of the skin have been involved, as is usual, pitting follows with permanent scarring, but not every case results in scars Pocks may be followed by temporary hyperemia only, with eventual return to normal skin.

VARIETIES OF SMALLPOX

Much the commonest type of fully developed smallpox is the form with the lesions for the most part separate and discrete although those on the face may be semi-confluent Variations in the number of lesions are great, from a few small pustules scarcely enabling a diagnosis to many thousands covering the entire skin surface In addition there are several distinct types of the disease

1 **Confluent Smallpox** —In confluent smallpox the manifestations from the onset are severe, and the eruption is rapid in development and so extensive as to form a continuous purulent involvement of the skin Swelling of the underlying tissue is marked and the head, hands, and feet may be misshapen and very painful The mucous membranes are extensively involved and the constitutional manifestations of the suppurative stage usually marked, with delirium, extreme prostration, and also septic complications in most instances. The mortality of confluent smallpox is naturally very high When recovery occurs it is only after a long and desperate struggle

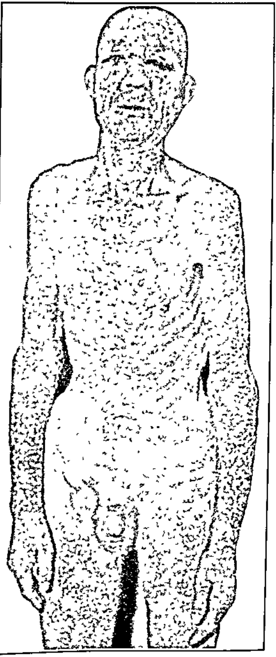


FIG 48 —Patient with pustular eruption of smallpox (Rivers, Viral and Rickettsial Infections of Man courtesy of J B Lippincott Company, and the National Foundation for Infantile Paralysis, Inc)

admitted one midnight to the contagious disease hospital as a hemorrhagic case of measles because of high fever, conjunctivitis, a very foul, bloody mouth, and an almost universally distributed elevated confluent purplish eruption. The next day a single discrete but typical early pock was found behind one elbow in about the only patch of otherwise clean



FIG. 49.—Confluent smallpox and varioloid. Two sisters suffering from smallpox. The one on the right, aged fourteen years, was successfully vaccinated in infancy, she contracted a mild varioloid and recovered without any scarring. The other, unvaccinated, developed a severe smallpox, confluent on face and arms, finally recovering, although considerably pitted. (Schamberg and Kolmer, Acute Infectious Diseases.)

skin on his entire body. Over 200 possible contacts in the hospital were vaccinated that day and none developed secondary smallpox. The patient died the next day.

3. **Alastrim (Amaas).**—*Variola Minor.*—This is a mild form of smallpox occurring in unvaccinated people. In the last forty years it has become increasingly common both in the United States and England. The incubation period is usually somewhat prolonged and may last even twenty or twenty-

2. **Hemorrhagic Smallpox.**—This may be divided into two types, according to whether the hemorrhagic manifestation appears in the invasive period or comes on during the eruptive stage. Why one case develops a hemorrhagic form of the disease and another does not is not known. It is probably partly due to variations in individual makeup, but an unusually toxic strain of the virus may also be responsible, because in some epidemics a higher percentage of hemorrhagic cases is found than in other epidemics.

(*a*) *Purpuric Smallpox, Black Smallpox, or Variola Purpurica.*—This is the most malignant form of the disease. The incubation period is usually shortened to seven or eight days. The onset is violent, with marked collapse and extreme severity of symptoms. By the second day petechiæ and purpura appear, followed by hemorrhages from the mucous membranes. Death is almost inevitable before the sixth day, but may occur within three or four days of the onset of the disease, even before the earliest manifestations of the usual eruption. The first case of an outbreak, as in that of New York City in 1947, is apt to be malignant and difficult to recognize. Death may occur before the correct diagnosis of smallpox is made either from autopsy findings or from the development of secondary cases.

(*b*) *Variola Hæmorrhagica Pustulosa.*—The more common form of hemorrhagic smallpox is characterized by hemorrhages into the pocks in the papular, vesicular, or pustular stage of the development. This form of hemorrhagic smallpox is only slightly less fatal than is purpuric smallpox, but is somewhat more prolonged, death usually occuring toward the end of the second week. Hemorrhages from the mucous membranes are usually present. This type of the disease is apparently more apt to affect those who are debilitated by previous illness, old age, or alcohol.

In the spring of 1918, a soldier of the British base troops, age fifty-four who had last been successfully vaccinated in infancy, was taken severely ill with high fever, headache, and great prostration. After an uncertain number of days he was

benign course. Most of these patients escape without any permanent scarring As in alastrim, the total course of the disease is appreciably shortened

Thus, while the manifestations of alastrim and varioloid may be quite similar, the former is a consistently mild disease, occurring in susceptible individuals, while the latter is true smallpox modified by a partial immunity in the patient. Incidentally, varioloid transmits unmodified smallpox to the unvaccinated

THE COMPLICATIONS OF SMALLPOX

1. *Secondary Infections of the Skin* —These are as variable as they are common Impetigo is present so frequently as to be considered part of the symptomatology by some of the writers Boils also occur in most of the confluent cases, particularly in the stage when the crusts are being shed, that is, in the fourth week of the disease Subcutaneous abscesses are also fairly frequently met, and bedsores and localized areas of gangrene may occur. Erysipelas, especially of the face, may develop during the second or third weeks, but is not as common as might be expected

The occurrence of pocks in the ear canal may cause distressing inflammation and even temporary loss of hearing through obstruction of the canal Otitis media during the suppurative stage is not uncommon in children

The conjunctiva of the eyelids is a common site for the pocks, which do not usually appear on the eyeball itself However, there is ordinarily a diffuse conjunctivitis with edema, and in some cases ulceration of the cornea may develop.

2. *Mucous Membrane Complications* —When there are pocks in the larynx, edema of the glottis may develop and cause even dangerous obstruction to respiration Ulceration of the larynx, edema of the tongue, nasal obstruction, and gangrene of the vulva have also been described

one days. The disease is characterized by a very variable period of onset, in some cases approximating the severity of the average case of smallpox, in others hardly sufficient to cause the patient to stay in bed In either case the ensuing eruption is comparatively sparse and mild, and the lesions do not ordinarily go on to the frank pustular stage. A normal temperature is not unusual after the rash has appeared and the total duration of the disease is often less than three weeks.

This form of smallpox is due to a mild strain of virus which breeds true and apparently never reverts to the old virulent strain of smallpox. Immunologically the alastrim virus is indistinguishable from the virus of smallpox, vaccination protecting against alastrim as well as variola, and alastrim, like smallpox, giving an immunity to vaccination which ordinarily lasts many years; but whereas the virus in smallpox produces a toxin which seems to further the growth and activity of such pyogenic organisms as streptococci, in alastrim these powers appear to be essentially absent Thus, alastrim is smallpox without the greater part of its toxicity and usually without streptoccus complications. The mortality from alastrim is in some epidemics less than 1 per cent.

4. **Varioloid.—Modified Smallpox.**—This is the term applied to those cases of smallpox which develop in individuals who have been vaccinated at some time in the more or less remote past, and who have lost some of the protection provided by that immunization These cases vary in their severity according to the degree of susceptibility of the individual but, in general, are characterized by an invasive stage which is quite similar to that of the normal case of smallpox, although frequently this stage is shortened to two days or even less With the development of the eruption there is often no subsequent rise in temperature and the further course of the disease is short and comparatively mild, unless there are complications, which, however, are comparatively uncommon. The usual toxicity of the disease is notably absent, and even confluent eruptions may run a comparatively

and a subsequent histological examination of the lesion may reveal Guarnieri's bodies Material from the pocks of varicella causes no lesions.

4. *The Complement-fixation Reaction of Parker and Muckenfuss.*—By means of this reaction and the use of a specific immune serum obtained from inoculated laboratory animals, pock fluids from lesions of vaccinia and of smallpox when collected before the thirteenth day of the eruption have given uniformly positive results. Under optimum conditions a report can be obtained in a few hours, but the pocks must be sufficiently advanced to contain fluid

5 *The Flocculation Test* —Fairbrother states that this test has been used for the diagnosis of variola with good results It involves the use of hyperimmune serum, and is not reliable until after the first week of the infection.

6 *The Vaccination Test* —Vaccination, if done after the onset of an eruption in an unvaccinated person, will fail to react if that eruption is part of smallpox

The presence of a good vaccination scar, particularly if not many months old, is a strong argument against the diagnosis of smallpox The reliable history of a very recent immune reaction to vaccination practically eliminates the possibility of smallpox.

Influenza.—In the period of invasion, the resemblance of smallpox to a severe case of influenza is marked, in fact, the differentiation may be impossible for a day or two, but knowledge of the presence of one or the other disease in epidemic form may be helpful If there is no evidence of an eruption by the fourth day, the case is not likely to be smallpox.

Measles, Scarlet Fever, Toxic Erythema —The prodromal eruption occasionally seen in smallpox may be quite similar to the prodromal eruptions of measles or to the true eruptions of scarlet fever or of other toxic conditions Further developments of an illness will usually clarify the diagnosis Severe measles with a confluent hemorrhagic eruption and marked constitutional manifestations may bear a strong

3. *Septicemia.*—Septicemia may occur as a result of infection with streptococci and before the days of antibiotics, was usually fatal

4. *Albuminuria.*—Albuminuria is present in most cases in the first week or ten days of the disease, but the clinical manifestations of an actual nephritis are unusual.

5. *Fibrinous pleurisy* is not unusual, but *lobar* and *bronchopneumonia* are not often met.

6. Complications due to involvement of the central nervous system are not especially common. Psychoses have been described, as also cases of encephalitis.

THE DIFFERENTIAL DIAGNOSIS OF SMALLPOX

The following specific tests for the diagnosis of smallpox have been described:

1. *Chick-membrane Test.*—By inoculation of the chorio-allantoic membrane of a chick embryo with blood or with fluid from a smallpox vesicle, a characteristic and recognizable pock is obtained in two or three days, but no reaction occurs from chickenpox (Iron *et al.*). English experts consider this the most reliable diagnostic test for smallpox.

2. *The Film Test of Van Rooyen and Illingworth.*—Delicate scrapings of early lesions are placed on a glass slide and stained by the Paschen method. Elementary bodies characteristic of smallpox were detected in 96 per cent of cases of smallpox, and there were no false positives as in chickenpox. A positive report is obtainable in about a half hour, and on the first day of the eruption. The electronic microscope, if available, enables easy differentiation of the elementary bodies of smallpox and chickenpox. (See page 337.)

The following tests are less valuable:

3. *The Eye Test of Paul.*—A needle dipped in a pustule or vesicle is used for scarifying the cornea of a rabbit. If the material on the needle was from a smallpox lesion, in thirty-six to forty-eight hours tiny vesicular lesions appear on the cornea and go on to epithelial necrosis and ulceration,

reactions have been employed extensively in proving the identity of the viruses of smallpox, alastrim, and vaccinia

All ages and all races are naturally susceptible to both variola and vaccinia, but through the immunization of the mother, some protection in the form of a congenital immunity can be transmitted to the unborn child. Such infants after birth may or may not react positively to vaccination But if the mother has never been vaccinated, a positive reaction is almost invariably obtainable in her infant There is no natural immunity.

Schick has shown that pregnant women, themselves immunized against smallpox by previous attacks of the disease or by vaccination, can give birth to pock-marked babies if exposed to smallpox during the pregnancy, without having evidence of ill health themselves. This would indicate tissue immunity but not humoral immunity in the mothers, and the passage of virus but not of antibodies from the mother's blood across the placenta to the fetus

Active Immunity.—Active immunity to smallpox can be acquired by.

1. A previous attack of smallpox or of alastrim Second attacks are very rare in proportion to the vast number of first attacks, but numerous cases have been observed, particularly in those who had their first attacks before puberty.

2 Inoculation with smallpox, a common procedure in many countries for centuries before Jenner's discovery of vaccination with cowpox There were many disadvantages to this method of immunization, particularly the occasional result of a fatal case of smallpox.

3. *Primary Vaccination* (see Chapter 13, page 363) —The duration of immunity against smallpox obtained from vaccination is approximately five to ten years, depending on the potency of the vaccine, the constitution or idiosyncrasy of the individual, and the number and size of the vaccination scars Revaccination not only furnishes a gauge of the amount remaining of an immunity, but also so markedly

similarity to the severe hemorrhagic forms of smallpox A titled young nurse's aid, seen during the first World War, had high fever, severe headache and malaise, and an eruption which very markedly resembled the confluent purplish eruption of an overwhelming case of smallpox that had been in the same hospital the week before (see page 348); she also had a twenty-year-old vaccination scar The appearance of Koplik's spots which was somewhat delayed, was greatly welcomed

Chickenpox —The clinical differentiation is discussed in the chapter on Chickenpox (page 325)

Rickettsial Pox —(See page 328.)

Syphilis (Known in Past Centuries as the Great Pox).—The pustular lesions occasionally found in syphilis sometimes cause confusion with the pocks of mild smallpox. The systemic manifestations of syphilis are much more indefinite in onset and the eruption appears more gradually. The pustular syphilide rarely attacks the palms and soles, is quite varied in character and chronic in course, is more coppery in color and has other differences in appearance, though much the same cutaneous distribution as the lesions of smallpox. Blood tests will be positive for syphilis, and spirochetes can be found.

Skin Infections.—Impetigo, pemphigus, acne, furunculosis, may each bear some similarity to mild cases of smallpox

Drug Eruptions.—Bromides and iodides may cause extensive eruptions more or less suggestive of the exanthem of smallpox. The sulfonamides only rarely cause a vesicular eruption.

IMMUNITY TO SMALLPOX

The state of immunity to smallpox is usually associated with the presence of antibodies in the serum and in the tissue cells. The former can be readily demonstrated by means of the complement-fixation test, agglutination and flocculation reactions, and the neutralization test These immunity

1. The presence and age of a previous vaccination The disease may be little altered by a vaccination fifteen or twenty years old.

2 The nature of the current epidemic, whether it be alastrim or true smallpox.

3. The nature of the stage of invasion. A mild onset is almost always followed by a mild course

4. The nature of the exanthem Confluent eruptions are much more serious than the discrete.

5 The presence of hemorrhages Hemorrhages of any type, whether into the skin, into the pocks, or from the mucous membranes, all indicate an almost certain death

6 The presence of such complications as general sepsis, pneumonia, erysipelas, pregnancy or abortion and alcoholism, all of which gravely affect the outlook

7 The age of the patient Infancy and old age add materially to the gravity of the prognosis

8 The place in an outbreak The first case is often malignant and may not be recognized before death

THE PERIOD OF INFECTIVITY OF SMALLPOX

Smallpox is very highly contagious, perhaps more so than any other disease It has been generally considered communicable not only throughout its course until the complete disappearance of all scabs and crusts, but also during the incubation period, particularly the latter part Recently, British authorities, on epidemiological grounds, have felt that smallpox is not readily transmitted before the first day of the eruption, but in theory at least if not in fact, contagion is possible by the second day of fever when the secretions of the nose and throat contain the virus

ISOLATION AND QUARANTINE FOR SMALLPOX

A doctor on first recognizing a case of smallpox or suspecting its presence should communicate at once with the

adds to a diminishing immunity that a fatal case even years after revaccination is rare.

After an exposure to smallpox, vaccination must be done within twenty-four to forty-eight hours to bring full protection. Vaccination done later in the period of incubation of smallpox will give a good reaction but less and less protection, and if more than seven days elapse between the time of vaccination and the onset of the variolous exanthem, no benefit will be obtained from the vaccination. Thus, three unvaccinated Italian soldiers were in adjacent beds in the "skin ward" of a British general hospital at Rouen, in 1918. On the fourth day after his admission because of a supposed impetigo, the middle one was diagnosed as mild smallpox. The other two were at once vaccinated, but in due course developed both very active vaccinations and severe cases of smallpox, from which one died.

After the onset of smallpox, the later the vaccination the less will be the reaction, until by the fourth or fifth day of clinical manifestations smallpox has produced a complete protection against vaccination (Blaxall)

Passive Immunity.—The serum of vaccinated persons and of those convalescent from the disease can neutralize the virus; hence, immune serum can be used with considerable effect for rapid protection against the disease.

THE MORTALITY AND PROGNOSIS OF SMALLPOX

The death-rate of unmodified smallpox varies greatly in different epidemics, ranging from 20 to 50 per cent or more Among primitive peoples, particularly the black races, the mortality is apt to be very high. In varioloid and alastrim the mortality is usually almost *nil*, except in the presence of coincident complications.

Death is usually due to the overwhelming toxemia. The severity of the disease, and with it the prognosis, depend on a number of additional factors:

reaction (Also see Immunity to Smallpox, page 354, and Vaccination Against Smallpox, Chapter 13, page 363.)

Convalescent serum, if added to a suspension of smallpox virus, renders the virus incapable of infecting the chick embryo Hence gamma globulin, especially if prepared from the blood of immune people, might well be given to susceptible contacts of cases of smallpox, particularly if their presumptive incubation period is already too well advanced to permit vaccination to be still of protective value.

THE TREATMENT OF SMALLPOX

The treatment of smallpox logically can be divided into the following general headings: the technic of the isolation of the patient; the specific treatment; the general treatment, and the detection and treatment of possible complications

1. **Isolation.**—The proper isolation of a case of smallpox requires such meticulous exactitude of detail that it can hardly be accomplished in a home or even a general hospital, hence all smallpox patients should be promptly isolated in a hospital properly equipped in personnel and facilities for handling such cases The wards or rooms should be screened, free from vermin, and well removed from the quarters of patients with other diseases. A medical aseptic technic should be put into effect which would militate not only against contact infection but also against possible insect-borne and air-borne infections The nursing and service personnel should be rigidly isolated in the building and grounds of the smallpox pavilion, and the medical personnel also if possible If a doctor must enter and leave a contaminated area he should use such extreme measures of precaution as wearing rubbers over his shoes while in the infected unit.

Concurrent disinfection of all discharges from a patient should be rigidly observed No article may leave the surroundings of a patient without being boiled for thirty minutes or undergoing other and equally effective disinfection.

local health authorities, so that there may be no delay in the isolation of the case, in the immunization of contacts, and particularly in the investigation of the source of the infection and the search for hidden unrecognized cases.

All patients with smallpox *should be isolated* in hospitals in screened wards, free from vermin, until the period of infectivity is past.

All persons who have had any possible contact with the patient or his effects should be isolated until proved immune by (1) vaccination with virus of full potency and (2) daily medical observation until the height of the vaccination reaction has passed, *provided* that the vaccination was performed not later than within twenty-four hours of the first exposure. Otherwise those exposed should be isolated for twenty-one days from the last exposure.

PROPHYLAXIS AGAINST SMALLPOX

Vaccination done after an exposure but yet early enough to have passed the height of its reaction (approximately the ninth day, if a normal vaccination) before the end of the incubation period of smallpox (approximately twelve days) will give complete protection. Hence, for complete protection, *vaccination must be done within about the first twenty-four* hours after an exposure, but a partial protection with modification of the subsequent attack of the smallpox may often be obtained from vaccination done even several days later (Schamberg and Kolmer).

To insure against possible failures through impotent virus or faulty technic, three or four vaccinations with different preparations of virus are advisable, particularly for exposed persons previously not vaccinated.

Vaccination in early infancy, with revaccination on entering a school, and again around the time of puberty, as well as whenever exposed or likely to be exposed, will give reasonable certainty of protection through life. In such a series of vaccinations, probably the first one only will give a full

reaction (Also see Immunity to Smallpox, page 354, and Vaccination Against Smallpox, Chapter 13, page 363)

Convalescent serum, if added to a suspension of smallpox virus, renders the virus incapable of infecting the chick embryo. Hence gamma globulin, especially if prepared from the blood of immune people, might well be given to susceptible contacts of cases of smallpox, particularly if their presumptive incubation period is already too well advanced to permit vaccination to be still of protective value.

THE TREATMENT OF SMALLPOX

The treatment of smallpox logically can be divided into the following general headings the technic of the isolation of the patient; the specific treatment, the general treatment, and the detection and treatment of possible complications

1 **Isolation.**—The proper isolation of a case of smallpox requires such meticulous exactitude of detail that it can hardly be accomplished in a home or even a general hospital, hence all smallpox patients should be promptly isolated in a hospital properly equipped in personnel and facilities for handling such cases The wards or rooms should be screened, free from vermin, and well removed from the quarters of patients with other diseases A medical aseptic technic should be put into effect which would militate not only against contact infection but also against possible insect-borne and air-borne infections The nursing and service personnel should be rigidly isolated in the building and grounds of the smallpox pavilion, and the medical personnel also if possible If a doctor must enter and leave a contaminated area he should use such extreme measures of precaution as wearing rubbers over his shoes while in the infected unit.

Concurrent disinfection of all discharges from a patient should be rigidly observed No article may leave the surroundings of a patient without being boiled for thirty minutes or undergoing other and equally effective disinfection.

local health authorities, so that there may be no delay in the isolation of the case, in the immunization of contacts, and particularly in the investigation of the source of the infection and the search for hidden unrecognized cases.

All patients with smallpox should be isolated in hospitals in screened wards, free from vermin, until the period of infectivity is past

All persons who have had any possible contact with the patient or his effects should be isolated until proved immune by (1) vaccination with virus of full potency and (2) daily medical observation until the height of the vaccination reaction has passed, *provided* that the vaccination was performed not later than within twenty-four hours of the first exposure Otherwise those exposed should be isolated for twenty-one days from the last exposure.

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For the local treatment of the skin lesions, many remedies are variously recommended, the general purposes being to mitigate the pain and itching, to overcome the foul odor of the exudate, and to prevent further infection Attempts are also aimed at reducing the liability of permanent scarring but no successful preventative other than the prevention of the disease itself by vaccination has been found. Carbolated petrolatum, calamine and zinc lotion, dusting powders or ointments containing sulfonamides or antibiotics, all are variously recommended

The lesions of the mucous membranes also require special attention. The mouth should be cleansed frequently with [illegible]

acid or weak saline solutions, and it is very important that the lid margins be kept lubricated with boric acid ointment or a sulfathiazole or antibiotic ophthalmic ointment Lesions about the genitalia will also require special care

In the severe cases particularly, the maintenance of the patient's strength is sometimes very difficult Lesions in the pharynx make swallowing very painful and great resourcefulness is necessary to help the patient receive adequate nourishment, especially if intravenous injections are prevented by the septic condition of the skin over the veins The fluid requirements must somehow be satisfied In fact, the skill shown in the care of a patient may frequently be the determining factor in the outcome of the case When convalescence has been established, careful consideration is still necessary for combating the secondary anemia, and building up the general strength of the exhausted patient

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The isolation of a patient must be continued until all scabs and crusts have disappeared, a period usually of four to six weeks. Before release from isolation he should be given one or more unusually thorough antiseptic baths, including the scalp. After his release his premises must be scrupulously cleaned and disinfected.

2. **Specific Treatment.**—There is no specific drug for the cure of smallpox nor other specific remedy. The sulfonamides and antibiotics have no effect on the manifestations of the disease due to the virus, but may both prevent and cure the commonly concurrent secondary infections

3. **The General Treatment of the Patient.**—In the general care of a case of smallpox, attention should be directed along three lines: the comfort of the patient, the local treatment of the lesions of the skin and mucous membranes, and the maintenance of the patient's strength. Nursing care is usually more important than medication.

During the invasive stage the patient is ordinarily very miserable and sedatives are indicated. The headache may be alleviated by ice-bags and the backache by heat Sponge baths are soothing and aid in reducing the high fevers occasionally met in this stage In the early eruptive period the patient may be quite comfortable, but when the eruption is vesicular and later purulent, distress is often very great and sedatives are again indicated. For treatment during the height of the eruptive stage, some authorities prefer no topical applications and even no bathing On the other hand, Schamberg and Kolmer strongly advocate continuous warm baths, cases of confluent smallpox being kept in water at approximately body temperature for several days. Fever is lowered and delirium relieved. During the stage of pustulation and desiccation baths are recommended in very weak solutions of antiseptics to wash away the purulent exudate and perhaps diminish the liability to secondary skin infections.

Injury to troublesome lesions on the back can be reduced by the use of an air-mattress, and cradles to hold the bedclothing off the skin are also comforting.

13

Vaccination Against Smallpox

Definition.—Vaccination against smallpox is accomplished by inoculating the skin of susceptible people with a virus usually prepared from the pock contents of calves suffering from an induced cowpox. The result of a successful primary vaccination is called "*vaccinia*" from the Latin word "vacca" meaning cow.

Smallpox virus which causes in man a highly contagious disease can, by means of repeated passages in animals, be modified into vaccine virus which incites in man a non-contagious disease—that is, non-contagious except in the presence of such preëxisting skin inflammations as infantile eczema.

THE HISTORY OF VACCINATION

For centuries smallpox was the scourge of all the countries of the world, killing thousands of people yearly in each large nation. People who were not pock-marked were in the minority in most communities. By the early part of the eighteenth century the Turks knew that when the disease was contracted by inoculation through an abrasion in the skin it was much less virulent and the mortality was much lower than when the disease was contracted by the usual contact. Hence they had developed the practice of inducing immunization against the disease by inoculating the skin of susceptible people with virus obtained from smallpox patients. Lady Mary Wortley Montague, the wife of the British Ambassador to Turkey, introduced the procedure into England in 1718 and was largely instrumental in establishing the

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[illegible] Test for [illegible] pox [illegible] et, 2, 67, 194[illegible]

Also see page 384.

Finally, on May 14, 1796, he inoculated an eight-year-old boy, James Phipps, with virus from a cowpox lesion on the hand of a dairy maid, and on July 1 he inoculated the same boy with the contents of a pock of a smallpox patient, without the boy's developing smallpox. After further experiments he published in 1798 a treatise entitled "An Inquiry Into the Causes and Effects of the Variolæ Vaccinæ," in which he described the method of cowpox vaccination and the resulting protection against smallpox. This publication at once attracted great attention in England, and very soon thereafter in all the civilized countries of the world. When the effectiveness of vaccination became apparent to all, Jenner was granted such honors as have been accorded few people in the history of mankind. He died in 1823 at the age of seventy-three years.

Vaccination was introduced into the United States in 1800 by Dr. Benjamin Waterhouse, of Harvard University, and the procedure spread rapidly in this country. However, there was strong opposition at the start, and even after one hundred and fifty years since Jenner's first vaccination, though the great value of the procedure has been clearly established, vaccination still has its opponents. Nevertheless, it has been declared the greatest of all boons to the human race.

THE VIRUS

1. **The Nature of the Virus.**—The relationship of "cowpox," a disease of cattle, to "smallpox," a disease of mankind, has been the subject of much discussion and research. There is now reliable evidence to prove that smallpox is converted into cowpox by passage through the tissues of cattle. In other words, the virus of cowpox is now recognized as the virus of smallpox in an attenuated or modified form. (See Chapter 12, Smallpox, page 336.)

2. **The Preparation of the Virus.**—For many years after the procedure of vaccination was established, vaccination virus was obtained not only from the pocks of cattle, but fre-

practice in Europe In Boston, in 1721, Zabdiel Boylston inoculated his own son and two slaves with the virus of smallpox. He met great opposition among the other doctors, but persisted with the inoculations, being ably backed by the Reverend Cotton Mather in his sermons. The induced disease was not always mild, however, and a small percentage of the inoculated patients died. Furthermore, the inoculated disease was a source of contagion to others, and so this procedure did not become widely practised.

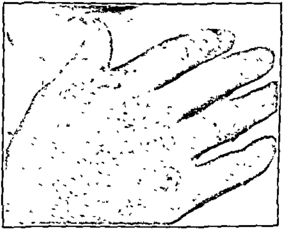


FIG 50 —Cowpox lesions on hand of farm worker infected during milking of cows (Downie and MacDonald, courtesy of British Med Jour)

In various rural communities through parts of Europe, and especially in Gloucestershire in England, the impression was current in the latter part of the eighteenth century, that when milkmaids and farmers developed infected hands from the lesions on the teats of cows which were suffering from cowpox, an immunity against smallpox was conferred upon these people by this infection. A young medical student, named Edward Jenner, learned of this tradition from a dairymaid, and for a number of years made observations which apparently confirmed the reality of this protection.

Despite these guarantees of purity and safety of calf virus various workers have endeavored to obtain by culture an active agent that is free from bacteria and contaminating viruses, and that will protect human beings against smallpox with a minimum of discomfort. Rivers and others have found that the virus of vaccinia will grow well on a medium containing living chick embryo tissue suspended in Tyrode solution, and that the virus obtained after many culture passages, when used for intradermal vaccination is not only safe and satisfactory but also protects against standard dermal vaccination done with the usual calf lymph and *vice versa* Somewhat similarly, Goodpasture and Buddingh have prepared a vaccine by culturing virus in the chorio-allantoic membrane of chick embryos in their shells. No complications or sequelæ of any kind have been reported following the use of chick vaccine virus and its use seems to be followed by a slightly milder clinical course than the use of calf virus However, present day calf-virus vaccine is so uniformly reliable, it is in universal use

The use of a living virus is essential for the production of a high degree of immunity against smallpox, and a good vaccine is protective against all strains of smallpox virus Virus killed in various ways has been tried experimentally but the results have been unreliable and inconsistent The stability of vaccine virus is not high At "room temperature" the average life of the virus is only *from one to three weeks*, and the incidence of "takes" is reduced 50 per cent At summer heat its complete value will be lost within three days Vaccine virus should be constantly stored at a temperature below 40° F. (5° C) and its potency should not be trusted after three months. Dry ice should be used for transportation

NEED AND INDICATIONS FOR VACCINATION

A community which is 100 per cent vaccinated will have no smallpox except that which is introduced from without It is obviously the duty of every individual, not only to

quently from the pocks of people who had been either infected directly from cattle or vaccinated. This human lymph occasionally contained secondary contaminations, and cases were reported where syphilis or tetanus was transmitted by this procedure Naturally enough, this gave good cause for much of the opposition that continued through the nineteenth century. As the virus is prepared at the present time, there is no possible danger of these diseases being given by vaccination. The bellies of young calves are cleaned according to surgical technic, and then extensive inoculations are made with an active virus, either human or calf in origin The inoculated area is usually protected by dressings, and after six days, when the vesicles have formed all over the inoculated area, the calf is killed and the contents of the vesicles are curetted off into sterile containers. The lymph that seeps into the curetted pocks is also used. The material thus obtained is mixed with five times its weight of a preparation of glycerin and water (50 per cent glycerin, 49 per cent water, 1 per cent carbolic acid), and the glycerinated pulp is allowed to stand for three or four weeks. The effect of the glycerin is to cause the destruction of any contaminating bacteria, and also to dilute the bulk of the lymph without appreciably interfering with its activity

At the end of four weeks the glycerinated lymph is subjected to culture experiments to prove the absence of all contaminating organisms Since the calf is not subject to syphilis there is no danger of transmitting this disease. The vaccine laboratories of the United States are carefully inspected by an official of the Hygienic Laboratories of the United States Public Health Service, which also requires that each vaccine institute perform a careful autopsy on each calf after the vaccine virus has been removed If any communicable disease is found or suspected in the animal, the virus must not be placed on the market, but must be destroyed. Incidentally, no other virus is known to be pathogenic for both cattle and human beings

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The use of a living virus is essential for the production of a high degree of immunity against smallpox, and a good vaccine is protective against all strains of smallpox virus. Virus killed in various ways has been tried experimentally but the results have been unreliable and inconsistent. The stability of vaccine virus is not high. At "room temperature" the average life of the virus is only from one to three weeks, and the incidence of "takes" is reduced 50 per cent. At summer heat its complete value will be lost within three days. Vaccine virus should be constantly stored at a temperature below 40° F. (5° C.) and its potency should not be trusted after three months. Dry ice should be used for transportation.

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himself but to the community in which he lives, to keep himself immunized against a disease which can, in severe epidemics, kill one-half the people afflicted, and even one-tenth of the population of an unprotected city.

In the presence of an epidemic, everybody must be vaccinated, regardless of the time when the last previous vaccination was done, unless the scab of a recent vaccination is still present. The mere presence of a scar of an old vaccination does not tell how old that vaccination is, and it is far wiser to make sure that the individual is immune than to presume that a former immunity is still present

In the absence of an epidemic, babies should be vaccinated sometime between the third and fifteenth months. Newborn infants are definitely more difficult to vaccinate successfully than older children—in part due to a humoral transfer of antibodies from the mother, but probably more because of tissue insusceptibility Nevertheless, if a sufficient number of attempts are made, nearly all newborn infants can be vaccinated successfully. However, *vaccination during the first two months of life may produce merely a mild though prolonged reaction which may or may not protect against repeated vaccination several months later. Therefore, probably the best time for primary vaccination is the latter half of the first year Revaccination should be done when the child enters school at five or six years, and when* puberty is reached If this is done he can be assured of a protection certainly for the better part of his life but revaccination every five years is desirable Additional vaccinations should be performed before a round-the-world cruise or any trip into countries where smallpox is endemic, such as China, Russia, India and Mexico, and various sections of the United States If there is a choice, a time should be chosen [illegible]

[illegible] ie presence of an [illegible] Babies may be [illegible] nts *suffering from* [illegible] *other contagious diseases certainly should be vaccinated if*

they are to be admitted to a hospital where they may possibly be exposed to smallpox. In the absence of an epidemic it is well to postpone vaccinating children afflicted with such skin diseases as eczema, impetigo, and furunculosis. Infants already suffering from severe gastro-intestinal upsets or marked malnutrition may well be spared the slight added burden of vaccinia until they are appreciably stronger.

People with "taking" vaccinations are definitely contagious Therefore, since babies with infantile eczema can develop severe generalized vaccinia following exposure to a brother or sister with vaccinia it is well either not to vaccinate the sibling or else to isolate the susceptible infant

Vaccination of women during the first trimester of pregnancy significantly increases the fetal mortality and so, if at all possible, should be avoided during that period There is no evidence that the percentage of abnormalities in full-term infants is increased by vaccination in the first trimester, and vaccination during the last six months of pregnancy apparently has no effect on the outcome

TECHNIC OF VACCINATION

1 **The Site.**—The site to be chosen for the inoculation should depend on several factors. In infants still in need of a diaper, the site should be one where the danger of wetting is slight As girls do not like conspicuous disfiguring scars, girl babies may be vaccinated 2 or 3 inches below the knee on the medial aspect of the leg, and older girls are usually vaccinated on the outer aspect of the thigh at a point about two-thirds of the way from the knee to the hip. Boys are usually vaccinated on the left arm at a point superior to the insertion of the deltoid muscle, and since scars resulting from the present method of vaccinating are rarely unsightly, girls might well be vaccinated there also.

2. **Number of Inoculations**—In certain European countries it is the custom to make three inoculations and in other countries four This is done in part so that there may be a

greater likelihood of at least one of the inoculations taking. There is also the theory, and a certain amount of statistical evidence to support it, that the greater the number of vaccination scars, the smaller the likelihood of contracting the disease. In the presence of an exposure, it is well to inoculate at two or three different points, and with different preparations of vaccine virus, but otherwise it is the almost universal custom in the United States to inoculate at one point only

3 **Procedure** —The skin of the area chosen is cleaned with soap and water, and then sponged with alcohol, which must be allowed to dry thoroughly. A drop of the virus is then placed on the skin and the inoculation is made through the drop. This may be done either with a sterile drill, shaped like a tiny screw-driver, which, while the skin is drawn taut, is rotated or twisted with moderate pressure so that it makes a circular abrasion without drawing blood, or a sterile needle may be used instead, and a tiny scratch not more than 2 mm long nor deep enough to draw more than a faint speck of blood may be made A needle is also used in the method known as "acupuncture," the procedure now favored by most authorities, wherein the side of the point of the needle is pressed into the skin through the drop, and flicked up a number of times, care being taken to press the needle in the skin in an area not more than 2 mm in diameter. A combination of these last two methods has given very satisfactory results. Following the inoculation, it is usually wise to have the patient wait in the presence of the doctor or nurse for a period of ten or fifteen minutes, ostensibly to give the virus a chance to dry, but really to prevent the patient, when out of sight, from applying some chemical to the area of inoculation in the hope of avoiding a "take"

The inoculation may also be done by injecting the virus into the skin in a manner analogous to the injection of the Schick test. This method is a little more trouble than the methods previously described, and there is the slight chance of the injection being subcutaneous and failing to give a scar.

Most health authorities refuse to recognize any method of vaccination which is not followed by scar formation.

4. **Dressing.**—There is much difference of opinion as to the advisability of putting a surgical dressing over the inoculated area. A shield certainly should not be used, especially one with a felt ring. Secondary infections are very common under these circumstances Leake and other authorities feel strongly that no dressing should be used, the ideal treatment being to keep the site cool and dry and to allow free circulation of the air over the lesion Dressings may adhere to the top of the vesicle or if attached around the arm may interfere with superficial lymphatic drainage However, inasmuch as in many young children the first symptom of a positive reaction is itching, many pediatricians believe that the vaccination should be protected during the period from operation to scab formation, by a sterile dressing so that dirty fingernails will be less apt to scratch it. A piece of sterile gauze fastened over the vaccination with two strips of adhesive plaster, in such a manner as to be "ballooned" away from the skin serves to keep some dirt away from the area, but fingers can still get under this covering The best dressing is probably made of two sterile folded gauze sponges, one upon the other, the one next to the skin having a window cut in its center by folding it in quarters and cutting off the folded point with sterile scissors These gauze dressings are securely fastened with two strips of adhesive, and with some children it may be advisable to put on two additional strips to fasten down the other borders If it is kept dry, this dressing may be left untouched until the sixth or seventh day, when the child is brought back for examination of the result. In case of a positive reaction it should be renewed and the vaccination kept covered until a hard, dry scab has formed

Care should be taken in applying the adhesive plaster so that it does not form a ring around the limb, thereby interfering with the circulation and with the usual swelling that accompanies a successful vaccination. The plaster of the first dressing should not be removed from the skin when the

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begun to form around it This red area becomes somewhat swollen and extends during the next day or two, becoming even 10 or 12 cm in diameter. The vesicle which is multilocular, and was at first fairly white, turns yellowish. By the twelfth day, the vesicle dries, leaving a brownish crust or scab, which seems to be set into the skin, and is tightly adherent. The redness clears up fairly rapidly, the swelling goes down, and after eighteen or more days the scab becomes detached, leaving a slightly purplish punched-out scar with a very slightly elevated center, irregular markings inside the margin, and a slightly elevated marginal ring. In the course of time the scar loses its color, and becomes much flatter, and after a period of two or three years, if the vaccination was done with a very small scratch, the scar may be difficult to detect from the surrounding skin.

The *symptoms* of vaccinia vary considerably in different people. About the sixth day, there may be twenty-four hours of fever and loss of appetite, even though the vaccination still looks quite innocent; a day or two later a child apparently feels quite well [illegible]
inflamed and sore.
to be very sore and [illegible]
very little about it, and infants are customarily disturbed hardly at all. As has already been stated, the first sign of a take may be itching at the area of inoculation, and the desire to scratch should be suppressed.

The *pathology* of vaccinia is similar to that of a characteristic lesion of smallpox. It begins as a papule which is the result of inflammatory changes in the epidermis, and as a result of cell liquefaction and intracellular edema the papule becomes a loculated vesicle made up of numerous compartments or [illegible]
[illegible]
the vesicle into a purulent fluid, thus giving rise to the pustule, which becomes unilocular as the partitions rupture The fluid and the necrotic epithelium gradually dry into a crust

dressing is changed but should be cut at the edge of the gauze. New plaster may be applied on top of the old tails, and all removed together when the final dressing is discarded.

For revaccinations likely to result in immune reactions, dressings are not indicated except perhaps to protect the moist fresh vaccination for an hour or two.

REACTIONS TO THE INOCULATION

1 **No Reaction.**—If there is no reaction other than that which follows any slight scratch in the skin, the assumption should be that there was something wrong about the vaccination, and it should be repeated There are a few people who have failed to show any reaction despite repeated inoculations, and accordingly a natural immunity must be considered but this is much less common than is indicated by the accounts of people who state that they have been vaccinated without a "take" The usual causes of failure to get any reaction are (1) a poor virus, one that was not kept sufficiently cold, or that was kept too long; and (2) an improper technic, in which the virus either was applied before the alcohol on the skin had dried, or was washed off immediately afterward by the application of an antiseptic or by too copious bleeding *from the site of the inoculation When there is no reaction* to an inoculation the assumption should be that no true vaccination has been performed.

2 **Primary Vaccinia, or a Normal "Take".**—If an individual has never been immunized by a previous attack of smallpox or by a previous vaccination, the reaction will manifest itself as a primary vaccinia. On the third or fourth day after vaccination a small reddish papule appears at the site of the inoculation, and about a day later the papule becomes a vesicle which is slightly larger than the inoculated area, and which surrounds and is slightly elevated above the scratch of the inoculation. This scratched mark becomes an umbilication as the vesicle enlarges, and by the seventh day the lesion is from 0 5 to 1 cm in diameter, and a red area has

begun to form around it. This red area becomes somewhat swollen and extends during the next day or two, becoming even 10 or 12 cm. in diameter. The vesicle which is multilocular, and was at first fairly white, turns yellowish. By the twelfth day, the vesicle dries, leaving a brownish crust or scab, which seems to be set into the skin, and is tightly adherent. The redness clears up fairly rapidly, the swelling goes down, and after eighteen or more days the scab becomes detached, leaving a slightly purplish punched-out scar with a very slightly elevated center, irregular markings inside the margin, and a slightly elevated marginal ring. In the course of time the scar loses its color, and becomes much flatter, and after a period of two or three years, if the vaccination was done with a very small scratch, the scar may be difficult to detect from the surrounding skin.

The *symptoms* of vaccinia vary considerably in different people. About the sixth day, there may be twenty-four hours of fever and loss of appetite, even though the vaccination still looks quite innocent; a day or two later a child apparently feels quite well at a time when the vaccination appears inflamed and sore. Adults usually find a taking vaccination to be very sore and uncomfortable, but children complain very little about it, and infants are customarily disturbed hardly at all. As has already been stated, the first sign of a take may be itching at the area of inoculation, and the desire to scratch should be suppressed.

The *pathology* of vaccinia is similar to that of a characteristic lesion of smallpox. It begins as a papule which is the result of inflammatory changes in the epidermis, and as a result of cell liquefaction and intracellular edema the papule becomes a loculated vesicle made up of numerous compartments or loculæ. The more pronounced swelling in the periphery causes the central umbilication. An outpouring of plasma cells follows, changing the originally clear fluid of the vesicle into a purulent fluid, thus giving rise to the pustule, which becomes unilocular as the partitions rupture. The fluid and the necrotic epithelium gradually dry into a crust

and healing takes place beneath the scab. On the fourth or fifth day, the leukocyte count usually rises to about 15,000; about the eighth day, this drops to even lower than normal, to rise again about the tenth day to slightly above normal. Immunologically, humoral antibodies to vaccinia begin to appear by the seventh day following vaccination and reach a maximum by the end of the third week.

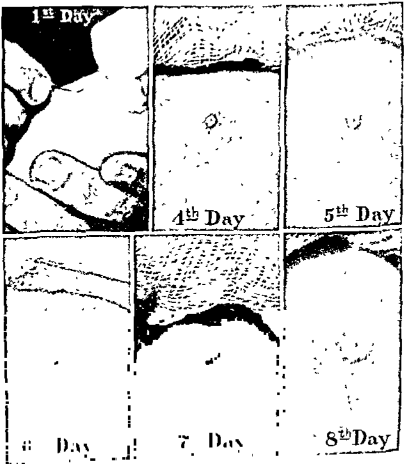


FIG 51 —Vaccinia, course of the eruption. (From Rosenau's Preventive Medicine, courtesy of D Appleton & Co)

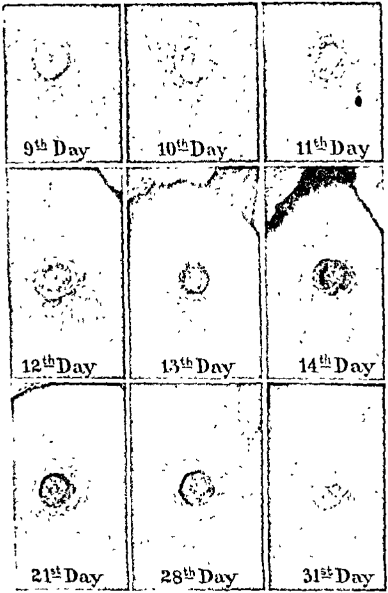


FIG 52 —Vaccinia, course of the eruption. (From Rosenau's Preventive Medicine, courtesy of D. Appleton & Co)

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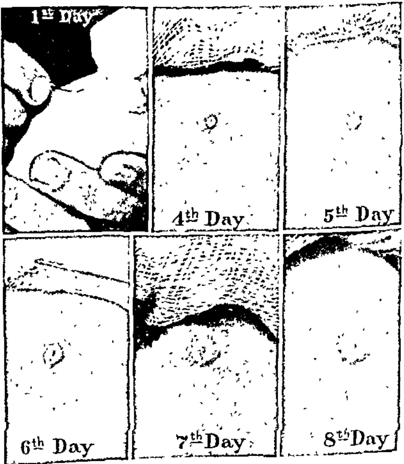


FIG 51 —Vaccinia, course of the eruption (From Rosenau's Preventive Medicine, courtesy of D Appleton & Co)

PLATE IX



Eczema vaccinatum

3 **Accelerated Reactions.**—These reactions, also called "vaccinoid" and "secondary vaccinia," are usually found in individuals who have been previously immunized, but have lost a considerable degree of the immunity. In these individuals the reaction is less than that of primary vaccinia, develops more rapidly, and disappears in a much shorter period of time The papule may appear by the third day. The vesicle is smaller in size, and when the reaction reaches its maximum intensity, somewhere between the fourth and eighth days after vaccination, the surrounding areola of redness is less extensive than in true vaccinia. The scab is usually quite small and the ensuing scar may be only 5 mm. in diameter, and may disappear entirely in a year or two.

During the next few days after primary vaccination, autovaccinations done by scratching the early vesicle of a primary vaccination and then some other place in the skin, also second vaccinations with a prepared virus, all cause a vaccinoid reaction which develops more rapidly than the original lesion and is matured by the ninth day, as is the original vaccination After the ninth day, primary vaccination gives an immunity against subsequent vaccinations.

4 **Immune Reactions** —If the individual has had smallpox, or has been successfully vaccinated and still retains a high degree of immunity, reaction to the virus will be greatly accelerated, and will become evident within a short time after vaccination. The reaction consists of a small area of redness surrounding the scarification, which reaches its greatest *diameter in from twenty-four to forty-eight hours after* vaccination A slightly indurated papule appears by the third day, but there is no transition from papule to vesicle, and no diffuse area of redness An immune reaction is doubly advantageous in that it gives evidence of an existing immunity to smallpox, and it re-inforces that immunity.

5. **Variations.**—Even as there are all degrees of immunity to smallpox, from none to complete, so there are also all the corresponding intermediate degrees of vaccination "*takes*," from a marked vaccinia to a definite early immune reaction.

In addition accessory vesicles may occasionally be found around the primary lesion at the site of inoculation, and in isolated instances small scattered papules and vesicles may appear in considerable number all over the body. This latter condition is sometimes called a "generalized vaccinia." (See below) A very rare progressive form of vaccinia spreading from the original focus has also been described.

With certain preparations of the virus, a small proportion of inoculations may be followed by the so-called "raspberry" form in which, as the name implies, the lesion is a red, irregularly shaped, excrescence elevated a little above the surface of the skin, and resembling somewhat a small vascular nevus. Neither red areola nor constitutional symptoms are present, and the course of a lesion is rather prolonged. Such a reaction is not supposed to confer immunity, but is thought to result from a different virus carried in the vaccine.

THE COMPLICATIONS OF VACCINATION

Vaccine virus after inoculation by any route has a tendency to become widely distributed in any tissue of the body and has been found in the blood of children several days after ordinary vaccination. It has also been isolated from the throats of vaccinated persons on the fourth and fifth days after vaccination (McKhann).

1. General Vaccinia.—Generalized vaccinia is a rare condition characterized by the appearance of widely distributed lesions similar to vaccinoid or accelerated reactions, but occurring spontaneously several days after a primary vaccination. The resulting eruption may strongly resemble varioloid, but has never been known to convey smallpox. Pitted scars seldom result from generalized vaccinia

Children with a tendency to infantile eczema are quite liable if vaccinated to develop a generalized vaccinia which may be confluent in large areas *Eczema vaccinatum* is a type of generalized vaccinia which occurs in patients suffering from extensive skin conditions such as eczema, intertrigo,

5 **Tetanus.**—Infections with the tetanus bacillus have been described. It is conceivable that contamination of the lymph at the time of collection might occur, but glycerination counteracts any such possible contamination. The Hygienic Laboratory of the United States Public Health Service, in approximately 100,000 examinations of vaccine virus never succeeded in finding any evidence of the presence of the tetanus organism or its products. Various shields that have been sold for vaccination have been found to contain tetanus bacilli, however. Otherwise, there is no longer any danger of this infection being transmitted by vaccination.

6. **Syphilis** —Cases of syphilis have been reported resulting from vaccination with human lymph, but calves are not susceptible to syphilis and there is no possibility of this infection when the calf virus is used On the other hand, false positive reactions may occasionally be obtained if blood tests for syphilis are done one to six weeks after successful vaccination, but not after an immune type of reaction, nor, in general, is this an important factor in interfering with the serological diagnosis of syphilis

7 **Postvaccinal Encephalitis.**—From 1923 to 1929 about 400 cases of a symptom-complex known as postvaccinal encephalitis were reported from various countries in Europe, particularly Holland where for some months about 1 vaccination in 4000 was followed by this complication Since then there has been a gradual decrease in the incidence and at the present time cases are extremely rare, especially in the United States where up to 1947 only about 75 had ever been reported However, in New York City in 1947 when about five million persons were vaccinated in one month, there were 45 cases of post-vaccinal encephalitis, or an incidence of 1 case for each 110,000 vaccinations Practically all cases have followed a first vaccination The symptoms of this

vomiting, headache, and a stupor which may amount to

impetigo, or secondary syphilis, as a result of intentional or accidental vaccination The latter may result from contact *with a vaccinated person even just by droplet infection from* his nasopharynx and is apt to develop two to three weeks after the vaccination The resulting skin infection may be so severe as to resemble confluent smallpox and one in six or *seven will probably die*

2 **Autovaccination** —Autovaccination is not uncommon in young children when the pustule has been left uncovered The child scratches the vaccination with the fingernail and then scratches herself somewhere else, and these self-inflicted vaccinations have been seen quite commonly on the lip, the cheek, the forearms, and even on the eyelid. The course of the autovaccinations is accelerated (see page 376), and the scab becomes detached about the same time as that of the original vaccination, particularly since the course of the original vaccination may have become prolonged because of having been infected by the child's fingernail

3. **Eruptions** —*Eruptions not necessarily specific to the* vaccinia may appear any time after about the third day, even until the tenth day As after serum injections they may be urticarial or morbilliform, and limited to the arm or leg, or more widely distributed, or they may be erythematous and possibly with petechial hemorrhages; or they may be papulovesicular suggesting an abortive attempt at generalization (Blaxall) These are usually evidence of skin-sensitivity reactions and are not related to immunity to smallpox

4 **Secondary Infections With Pus-forming Organisms** — *These are not uncommon when shields are used,* or when the pustule has been broken by trauma. The reaction varies according to the infecting organism, and may become quite extensive. Furunculosis, impetigo, cellulitis, and erysipelas have been described. Occasionally the lymph nodes which receive the lymphatics that drain the area of the inoculation become swollen and tender and there may even be abscess formation

life and at one spot only. Otherwise there are no known methods of prevention

8. **Various Other Complications.**—Various other complications due to vaccination have been reported, but it has been difficult to determine whether their occurrence was merely a coincidence or was really due to vaccination. If 1000 children out of a group of 2000 were vaccinated one day, and 3 or 4 children in each 1000 were to come down with some sickness the next day, as is always possible, the parents of the 3 who had just been vaccinated would surely attribute the illness to the vaccination.

THE TREATMENT OF VACCINIA

Ordinarily no special treatment is necessary for a "taking" vaccination except to protect the lesion from trauma. Occasional persons, particularly adults, have considerable fever and prostration for which bed rest and sedatives are indicated Pyogenic infection of the lesion requires hot compresses and antibiotic treatment For generalized vaccinia and eczema vaccinatum the injection of "vaccinia immune gamma globulin",[1] 0 6 to 1 0 ml per kilogram of body weight, may prove of value, and secondary infections should be prevented by careful cleanliness and antibiotics

For post-vaccinal encephalitis, the administration of serum from recently vaccinated adults has seemed to give very good results and specific treatments to combat the various harmful manifestations may be lifesaving.

IMMUNITY RESULTING FROM VACCINATION

The immunity to smallpox resulting from vaccination, while not 100 per cent, is nevertheless very nearly complete,

[1] Vaccinia immune gamma globulin has been prepared and distributed

coma are the most constant symptoms, and there often are such evidences of meningeal irritation as convulsions, cramps, and even trismus, which may lead to confusion of the diagnosis with tetanus. In fact, meningitic, cortical, tetanic, brain stem, and lower motor neurone types have been described. Retention of urine is common. The various meningeal signs such as those of Kernig and Brudzinski are variably positive and there frequently are transient paralyses. The Babinski sign is usually positive, a point considered of high diagnostic significance The spinal fluid shows little or no change from normal, except that the pressure may be slightly increased and cell counts up to 300 have been observed In a few instances vaccine virus in small amounts has been recovered from the spinal fluid. Microscopic examination of the central nervous system reveals lesions characteristically situated in the white matter and consisting of perivascular cellular infiltration usually associated with perivascular demyelinization, the lesions being similar to those encountered in the encephalitis that occurs after various of the contagious diseases, particularly measles There is characteristically little if any destruction of the neurones. Death, which followed in from 30 to 40 per cent of the cases in Europe but in only 4 of New York's 45 cases, usually occurs from the third to the tenth day following the onset of the symptoms of encephalitis. Recovery when it takes place is usually within two or three weeks, but may take place quite rapidly, and residual disturbances are quite rare The cause of this complication is still unknown, but it has been attributed to the vaccine virus itself, to the activation of some other neurotropic virus, or to the clinical expression of an allergic reaction of the central nervous system with the virus acting as a sensitizing agent. Cases in children below one year of age are rare but have a mortality of over 50 per cent.

Accordingly various health authorities have recommended that primary vaccination be done in the second six months of

life and at one spot only. Otherwise there are no known methods of prevention

8. **Various Other Complications.**—Various other complications due to vaccination have been reported, but it has been difficult to determine whether their occurrence was merely a coincidence or was really due to vaccination. If 1000 children out of a group of 2000 were vaccinated one day, and 3 or 4 children in each 1000 were to come down with some sickness the next day, as is always possible, the parents of the 3 who had just been vaccinated would surely attribute the illness to the vaccination.

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IMMUNITY RESULTING FROM VACCINATION

The immunity to smallpox resulting from vaccination, while not 100 per cent, is nevertheless very nearly complete,

particularly when the successful vaccination has been comparatively recent Cases of very mild smallpox have been reported in people who have been vaccinated successfully within a year, but such instances are rare. In fact, comparatively few instances of smallpox have occurred within six



FIG 53 —Illustrating the protection against smallpox obtained by vaccination Three members of a family brought to the Philadelphia Hospital [illegible]

years of a good vaccination Probably in the vast majority of instances a successful vaccination in infancy, an immune reaction at six years, and perhaps an accelerated reaction at sixteen years give protection for life.

Proof of the efficacy of vaccination is plentiful in medical literature Schamberg and Kolmer present a vast amount

of statistical evidence taken from all over the world. For instance, following the general introduction of vaccination at the beginning of the nineteenth century, there was a sudden and striking decrease in the incidence and mortality of smallpox. In Sweden in the twenty-eight years before vaccination 2050 persons died each year from smallpox out of every 1,000,000 of population; during the forty years following vaccination out of each 1,000,000 of population the smallpox deaths averaged only 158 a year.

Similar evidence is found in the effect of a compulsory vaccination and revaccination law which has been well enforced in Germany since 1875 For over fifty years prior to it, the average yearly number of deaths from smallpox was 6663, and during the forty-eight years after that date, the average yearly mortality was 171 Germany, with rather more than one-half the population, had less total smallpox in the last fifty years before 1930 than the United States ordinarily had in one year. From 1919 to 1924 the cases of smallpox in the United States averaged over 50,000 a year, this country being exceeded only by Russia and British India, the figures for China not being available. During this period of six years, California alone had 25,651 cases, while Massachusetts, with a larger population but a well enforced school vaccination law, had only 126 cases Only thirteen of the states require vaccination for school attendance, and seven states actually prohibit compulsory vaccination.

The fact that physicians, nurses, and others, if recently successfully vaccinated, may live in smallpox hospitals with safety, is further proof of the efficacy of vaccination In the Philadelphia Hospital for Contagious Diseases, during a period in which over 9000 cases of smallpox were being treated, not one physician, nurse, or attendant, who had been successfully vaccinated or revaccinated prior to going on duty, contracted the disease.

ARGUMENTS AGAINST VACCINATION

Most of the arguments advanced against vaccination are founded either on profound ignorance of the subject, or on

actual false statements which have been innocently unsubstantiated or are intentionally misleading. The dangers of transmission of secondary infections are particularly stressed, but for the past several decades this risk has been at a minimum, and with the use of calf virus instead of human vaccinia virus, the transmission of syphilis has been rendered impossible. In recent years the possibility of a complicating encephalitis has been feared but this complication has again become very rare It is argued that improvement in general hygiene and sanitation alone has been responsible for the decline in the incidence of smallpox, but during the same period the incidence of such diseases as chickenpox, measles, and whooping cough has been in no way comparably improved Antivaccinationists maintain that severe smallpox does occur in those who have been vaccinated, but who are classified as unvaccinated because the eruption has concealed the scar This argument is of course untenable, as are most of the other statements made in opposition to the procedure.

The risks of vaccination should be no greater than the risks which follow any other scratch The most trifling break in the skin has been known to be followed by malignant infection, but ordinarily a scratch is not considered an appreciable source of danger Even should there be a slight element of danger involved, the benefits to be obtained are unquestionably very great in comparison to the possible harm which may ensue. It is every person's duty to himself and to the community to maintain a personal immunity against smallpox by means of vaccination Otherwise, the disease cannot be wiped out as it should be in any given community; and inasmuch as people cannot be depended upon voluntarily to seek vaccinal protection vaccination for everyone should be made obligatory by law.

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Also see page 361

14

Acute Bacterial Meningitis

I. MENINGOCOCCUS MENINGITIS

From the Greek word μῆνιγξ (meninx) meaning membrane

Synonyms.—Epidemic meningitis, Cerebrospinal fever, and Epidemic cerebrospinal meningitis

Definition.—An acute infectious disease caused by the meningococcus, and characterized by primary local involvement of the naso-pharynx, by secondary invasion of the blood, and finally by the production of a purulent meningitis which usually predominates in the very variable clinical manifestations

THE ETIOLOGY OF MENINGOCOCCUS MENINGITIS

Exciting Cause and Bacteriology.—In 1887 Weichselbaum identified the meningococcus as the cause of this special type of meningitis It is also called diplococcus intracellularis meningitidis, and Neisseria meningitidis It is a small Gram-negative diplococcus, which in stained smears closely resembles the gonococcus Meningococci occur as kidney-shaped micrococci, usually united in pairs, but also as solitary bacteria, in groups of four, and in small masses Their normal habitat is in mankind only and laboratory animals are not susceptible to true infections *via* the naso-pharynx The meningococcus is easily killed by heat, disinfectants, and ordinary drying, and its growth on artificial media requires the presence of an animal protein, such as beef infusion, serum, ascitic fluid, or blood. It is highly para-

sitic, and dies promptly under adverse conditions. In smears, the diplococci are commonly found within pus cells, but the proportion of these organisms inside leukocytes to those outside is an indication of the activity of phagocytosis, and thereby of the progress of the resistance to the disease, since phagocytosis is the chief mechanism of resistance. In 1915 Gordon and Murray classified meningococci into four groups by means of agglutination tests. Subsequent studies, however, showed that groups 1 and 3 could not be distinguished from each other, and the two are now grouped together as group 1 Group 2 was found to be non-homogeneous and a separate group 2a has been separated from it Group 4 is so rarely encountered as to be of no practical importance Group 1 organisms have been the most prevalent in epidemics, groups 2 and 2a have been more frequently isolated in inter-epidemic periods

Manner of Transmission.—This disease is probably transmitted only by contamination with the secretions of the nose and throat of a patient or of a healthy carrier. The portal of entry is quite probably the nose and throat, whence the infection is carried by the blood to localize characteristically in the meninges In some cases the infection may remain a septicemia without evidence of localization.

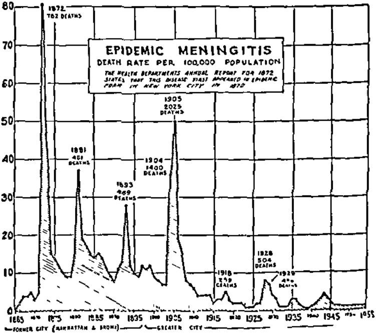
Localization.—The meningococcus may be found in the body in a number of different areas. It is found in the nasopharynx both of healthy individuals and of victims of the disease and may be found existing there as long as two weeks It is found in the blood in the so-called septicemic type of the disease and is probably always present there in the early stages of the disease Its particular affinity is with the meninges, and so it is found most readily in the spinal fluid, and at autopsies in the tissues of the central nervous system also. It may also be found in the secretions of the joints in cases of arthritis, in the lungs in patients with a meningococcic pneumonia, and occasionally in other local foci throughout the body as in the adrenals It is also to be found in the hemorrhagic lesions of the skin

Epidemiology.—The disease occurs both sporadically and epidemically, and epidemics have occurred in practically every civilized nation At times epidemics show a tendency to periodicity, appearing in cycles of ten to twelve years Meningococcus meningitis shows wide variations in its severity in different outbreaks The beginning of an epidemic is presumbly caused by the introduction of new strains into a more susceptible population, but most of the cases in a given epidemic are due to one type of organism The early cases in an outbreak are apt to have a high mortality, suggesting a rapid increase in the virulence of the particular meningococcus due to rapid passage from one extremely susceptible host to another Epidemics of this disease always are coincident with an increase in infections of the upper respiratory tract.

Most epidemics are characterized by two additional features not ordinarily seen in other epidemic diseases with the exception of poliomyelitis In the first place, widely separated localities are often simultaneously attacked when no connection between them is obvious, in the second place, the proportion of inhabitants contracting the disease in a clinically recognizable form is usually very small The occurrence of more than one case in a family is comparatively uncommon In an epidemic in Indianapolis, however, 30 out of 144 cases were instances of plural infections in 11 families, and 90 per cent of the early cases were employees or relatives of employees of one concern In an epidemic which we studied in Baltimore, 11 per cent of patients were secondary family cases

Season, Sex, Race and Age.—Both epidemic and sporadic cases are appreciably more common in the winter and early spring months than during the other seasons The predominance of males over females is marked There is apparently no particular racial susceptibility or immunity but this is a disease of the temperate and subtropical zones, cases rarely occurring in the tropics The disease occurs in all ages, but the great majority of cases are in children, except in instances

where adults are brought together from rural communities, as in army camps. In recent years, as with poliomyelitis, there has been somewhat of a shift to higher ages. However, more cases occur in the first year of life than in any other single year, and the mortality in the first year is the highest.



The youngest reported case had the onset on the ninth day (Koplik).

Carriers.—Although in the spread of epidemics the virulence and type of meningococcus present is of great importance, the chief factor in the spread seems to be the presence of carriers,

who especially during epidemics are comparatively numerous in the general population Under normal conditions the examination of a cross-section of the population may reveal 2 to 5 per cent of carriers; when 20 per cent or more is present an epidemic threatens; and in army cantonments the incidence of carriers may reach 87.5 per cent. However, an attack rate of as much as 1 per 1000 of a general population is rare, although in camps and cantonments the rate may reach 20 to 50 per 1000. The number of carriers developing from sporadic cases is probably low, and the meningococcus of carriers tends to clear up spontaneously, particularly in warm weather. Many carriers are apparently innocuous, and it has been generally observed that very few carriers develop the disease, their immunity probably having been due to frequent exposure to meningococci of low virulence Chronic carriers are often found to have some abnormality of the nose and throat, such as diseased tonsils or adenoids.

Because of the multiplicity and variability of carriers, it has been impractical to protect a susceptible person in the general population from exposure to this disease However, during World War II, when large groups were involved, as in army and refugee camps, the use of chemo-prophylaxis with sulfadiazine gave excellent results

THE PATHOLOGY OF MENINGOCOCCUS MENINGITIS

At the portal of entry, which is usually the nasopharynx, there are no characteristic lesions, and some manifestation of upper respiratory infection may or may not be present before the recognized onset of blood or meningeal infection From the respiratory tract the meningococcus invades the blood where it multiplies rapidly Clumps of meningococci often collect in the capillaries of the skin and of the serous membranes and their toxins injure the vascular walls thus enabling the cocci to escape and to become localized in the surrounding tissues Thus purpuric spots from 2 to 10 mm or more in diameter are formed in the skin, the peritoneum,

pericardium, pleura, etc A similar process occurs in the meninges where the bacterial emboli cause congestion, thrombosis of the blood vessels, and hemorrhage in the pia-arachnoid These changes are followed by the formation of a sero-fibrino-purulent exudate The process is not uniform over the entire brain, but involves most commonly the lateral surfaces and the parietal and occipital lobes, and particularly the meninges over the cerebellum In the early acute cases the involvement is more apt to be toward the upper surfaces of the brain, sparing the longitudinal fissure, in the more chronic cases the involvement is more confined to the base The meninges of the cord are also involved, and the inflammation in many cases extends by means of the spinal fluid into the ventricles If pus or adhesions block off the various openings of the ventricles (see *Plate X*) an obstructive hydrocephalus results The exudate furthermore surrounds various cranial nerves, which are apt to become swollen and congested, particularly the second, fifth, and eighth As a result of the involvement of the second cranial or optic nerve, and also as a result of inflammatory lesions of the eye itself, eye complications are occasionally a serious feature of the disease Similarly, as a result of inflammation of the eighth, or auditory nerve, ear complications, notably permanent deafness, are another dreaded feature Inflammation of the brain substance (encephalitis) is often present, and abscess formation with foci of meningococcic infections may also be found

Extrameningeal meningococcus infections may occur, especially in the joints, and endocardium The various body organs show the usual lesions of an acute infection Large hemorrhages into the adrenal glands are sometimes present in the fulminant cases, but more often only petechial hemorrhages are found, together with necrosis of the cells in the zona fasciculata of the cortex of these organs.

The blood in meningococcus meningitis shows leukocytosis with a high percentage of polymorphonuclears, as in any pyogenic infection.

PLATE X

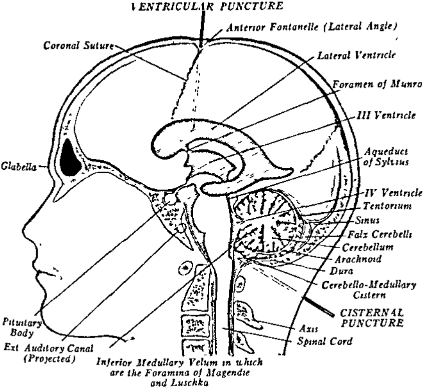


Diagram* to show the distribution of the cerebrospinal fluid in the ventricles and around the base of the brain (shaded area) and also the anatomical relationships involved in ventricular and cisternal punctures

* The drawing is based in part on ventriculograms provided by C W Schwartz, and on suggestions from the neuro anatomical viewpoint given by H A Riley

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The blood in meningococcus meningitis shows leukocytosis with a high percentage of polymorphonuclears, as in any pyogenic infection

IMMUNITY TO MENINGOCOCCUS MENINGITIS

The majority of people, particularly adults, apparently have a definite immunity to infections with the meningococcus, except at times when the organisms are of high virulence. Children are much more susceptible than adults, and Ferry has shown by a skin test that about 50 per cent of children are susceptible to the toxins of the meningococci.

Type-specific passive immunity of several weeks' duration may be obtained by use of antimeningococcus serum, but *prophylaxis with sulfadiazine* is much more practical and has entirely eliminated the necessity for this procedure. Active immunity is usually obtained from a previous attack of the disease, and presumably also by repeated submorbid exposures to healthy carriers.

INCUBATION PERIOD OF MENINGOCOCCUS MENINGITIS

The incubation period of meningococcus meningitis is probably quite variable, but in the majority of cases the incubation period ranges between three and seven days with only exceptional cases outside a one- to ten-day limit.

THE CLINICAL MANIFESTATIONS OF MENINGOCOCCUS MENINGITIS

Owing to great variations in the virulence of the meningococcus and in the resistance of the host, the evidences of infection with this organism are extremely variable. At the portal of entry, which is the nose and throat, no inflammation may occur, and signs of disease may be entirely absent, but the inapparent infection may bring about type-specific immunity. In other cases, evidence may be found of an upper respiratory infection with the usual symptoms of sore throat, fever and other systemic symptoms. It is probable that in many cases of meningococcus infection the disease is limited

four to forty-eight hours after onset. Dickason[1] has reported 4 infants in a Mexican epidemic that were seen by their parents at 11 P.M. in apparently good health, and were found cold in death at 5 o'clock the next morning In fact, death may occur before symptoms of involvement of the central nervous system have appeared. This type of overwhelming infection has been termed the Waterhouse-Friderichsen syndrome. It seems clear that the shock-like picture seen in this condition is in part at least due to injury to the adrenal cortex, which is described on page 420.

2. The Septicemic Type.—Septicemic cases of meningococcic infection are of two general types, acute and chronic. Of the *acute* cases some may be of the fulminating types just described, others only slightly less serious or rapidly progressive. Here the clinical manifestations are those of a severe blood infection. The patient is dull and apathetic, he resents being disturbed, and there is a distinct deviation from a normally alert mentality. Fever is irregular and quite characteristic of a septic infection. The most distinctive feature of this type of the disease, however, is the cutaneous hemorrhages, which may typically be petechiæ, either few in number and scattered almost entirely on the extremities, or much more numerous and distributed particularly about the neck and face, or they may consist of great purpuric blotches widely distributed all over the body. Petechiæ are also customarily present in the conjunctiva if present elsewhere. These cases are usually only slightly less severe and less rapid than are the fulminating cases, and without chemotherapy death is almost as inevitable Also, as is the case with the fulminating type of patients, some of the septicemia cases show no evidence of meningeal irritation while others go on to develop the clinical manifestations of the next type of the disease.

On the other hand, occasionally very mild cases of the septicemic type are seen in which the patients seem nearly normal except during periods of exacerbations of fever, especially

[1] J. A. M. A. 93, 1016, 1929

to the nasopharynx In others, however, the meningococci *invade the blood stream, and cause septicemia In some* septicemic patients the infection does not invade the internal organs However, in others emboli of meningococci cause thrombosis of the blood vessels of the meninges and meningitis results

Three main types of disease caused by meningococci may be described with many varieties of intermediate cases



FIG. 55 —Rash of meningococcemia (Hayne in Grulee and Eley, The Child in Health and Disease, courtesy of Williams & Wilkins Co)

1 **The Fulminating or Malignant Type** —These cases are characterized by an onset of overwhelming abruptness and severity, and an extremely rapid course. The attack is usually ushed in by chills or a convulsion, violent headache, vomiting, and high fever Purpuric spots appear in great numbers on the skin and in the conjunctivæ. Large ecchymotic areas develop rapidly on the trunk and extremities, and occlusion of blood vessels of varying sizes in the extremities may occur. The blood contains extremely large numbers of meningococci which may sometimes be seen in smears of the peripheral blood In some cases the blood pressure falls suddenly, the extremities become cold and clammy, and signs of *profound shock occur. Delirium and* coma may quickly follow, and death may take place in from

be in proportion to the temperature, but later is unusually rapid, and in rate and quality becomes a good indication of the degree of intoxication of the patient. A tâche cérébrale is present in possibly a third of the cases. The headache is usually diffuse all over the cranium, there often is marked hyperesthesia, and tremors of the extremities are occasionally seen. The mental condition varies from normal through all degrees of drowsiness, irritability, delirium, and stupor,

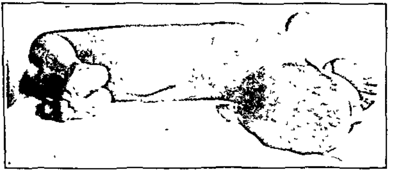


FIG 56 —Extreme opisthotonus in cerebrospinal meningitis (Schamberg and Kolmer, Acute Infectious Diseases)

to coma in the more severe cases In fact, meningitis is as common a cause of coma as diabetes or uremia, but in many cases of meningococcus meningitis with marked meningitic manifestations, not only may the mind be clear, but the patient may seem unusually alert

The most characteristic signs of the infection of the meninges are found in the musculature, evidenced by increase of tone or muscle spasm Stiffness of the neck varies in extent, but is usually quite marked, and sometimes the head is rigidly retroflexed Involvement of the other muscles of the spine produces a rigid posterior curving of the whole back, which is called "opisthotonus" and particularly in the late stages of meningitis is especially common in young patients.

evenings In fact, *chronic meningococcus septicemia* may be considered a distinct clinical entity characterized by headache, migratory joint pains, hemorrhagic skin eruptions, and intermittent chills and fever; manifestations which when occurring together should suggest the presence of a meningococcic infection If not made by blood culture as is often eventually the case, the diagnosis may be made or substantiated a week or two after the onset of the infection by a *positive agglutination of* meningococci *These cases run a* comparatively mild though very prolonged course and usually recover with or without sulfadiazine which, however, markedly shortens the course. They may, however, flare up into an acute meningitis

Furthermore, in the presence of an epidemic of meningococcus meningitis as in an army camp, what seem to be simple attacks of grippe should be suspected as possible early cases of meningococcus infection, particularly if restlessness and drowsiness become evident, if the headache increases, and soreness and spasm of the neck appear, and especially if the blood count shows a sharp increase in leukocytes in contrast to the leukopenia of grippe

3. **The Ordinary Type of Meningitis.**—The ordinary type of *infection with the meningococcus, or true "meningococcus* meningitis," is usually quite sudden in onset and begins with an irregular fever, intense general headache, vomiting, and rapid prostration Chills may occur, or there may be general convulsions, particularly in infancy In some cases the onset is gradual and *two or three days elapse before the clinical* manifestations are characteristic of the infection. The fever becomes quite irregular as is customary in most pyogenic infections, very great daily variations are sometimes met, and ranges of 8° to 10° in twenty-four hours have been observed At the height of the infection the respirations are usually markedly irregular in rate, rhythm, and depth, and the so-called Biot type of breathing, in which there are several rapid short breaths followed by a long pause, is of bad prognostic significance. The pulse-rate at first may

Among other features of this type of the infection are a tendency to retention of urine, constipation, marked loss of appetite, and a rapid wasting away in weight. In fact, prolonged cases of this disease, formerly not uncommon but now very rare due to chemotherapy, have shown great emaciation.

Meningitis does not always present so clear-cut a pattern as that just described. In fact, in infants and young children, very variable and indefinite clinical manifestations are frequently seen. The onset may be very insidious, with no symptoms pointing toward involvement of the central nervous system. Fever, irritability and refusal to feed are common symptoms, but these in no way point toward the location of the infection. Kernig's and Brudzinski's signs may be absent. Bulging of the anterior fontanelle may be the only indication of meningeal infection, and this may be equivocal. When the fontanelle is closed, this sign will, of course, be absent. It is very good practice to keep the possibility of meningitis in mind whenever one is treating an infant with fever of which the cause cannot be determined. In such cases a lumbar puncture may be needed to exclude the existence of meningitis.

Relapses occurring early or late in convalescence formerly were not uncommon and were often as severe as the original infection, but adequate antimicrobial treatment has cut the incidence of relapses practically to zero.

THE COURSE OF MENINGOCOCCUS MENINGITIS

The course of menigococcus infections is as varied as are the types of the disease. The fulminating cases may die before therapy can be instituted or before sufficient time has elapsed for treatment to be of benefit. The average case of the ordinary type of the disease is usually so clear-cut in its features that a diagnosis is readily made within twenty-four or forty-eight hours of the onset. With proper chemotherapy the course of such an attack of the disease now runs only a

The muscles of the back of the thigh are tense so that when the patient is lying on his back and a leg is flexed at right angles at both the hip and the knee, the hamstring spasm prevents the leg's being straightened at the knee, if the hip is still maintained at the right angle. This is Kernig's sign, and is of diagnostic importance in inflammations of the meninges Another important sign is Brudzinski's neck sign. Here the child is laid flat on his back and when the head is lifted and forcibly flexed on the chest, if the sign is present, the child flexes his legs at knee and hip and is obviously in distress. Brudzinski's name is also used in connection with the contralateral leg reflex which is positive and indicative of some central nervous system pathology if, when one leg of the supine patient is forcefully flexed on his abdomen, the other leg is flexed also.

The reflexes are somewhat variable. The knee-jerks are usually hyperactive but may become diminished or lost during the height of the disease to return during convalescence. The abdominal and cremasteric superficial reflexes are usually diminished or absent but also reappear with convalescence.

Skin manifestations in this type of the disease are quite variable. Herpes, particularly of the lips, are very commonly found, usually appearing from the fourth to the seventh day. The various forms of hemorrhagic eruptions which are described under the septicemic type of the disease may be found in this type also, particularly during the first two or three days, their persistence after this period may indicate that the blood infection is a marked feature.

Evidence of increased pressure due to the increase of the spinal fluid may be shown either by a bulging anterior fontanel if it is still open, by choking of the optic disks, or by MacEwen's sign. This sign is elicited by percussing over the lateral ventricle and is present when the sound has an increased resonance or hollow character and when the percussing finger detects a sensation of greater elasticity of the skull.

or around the foramen magnum this type of hydrocephalus is a general one

The infection may extend along the optic nerve causing optic neuritis, and the eyes may also be involved by a local or a blood-borne infection, so that iridochoroiditis and even meningococcic panophthalmitis may occur. Blindness may ensue, especially when the eye infection is of peripheral origin Involvement of other cranial nerves is seen, particularly of the third nerve giving rise to strabismus, of the sixth nerve preventing the eye from moving outward beyond the midline with resulting diplopia, and of the seventh nerve leading to facial spasm or weakness These paralyses usually clear up entirely after the infection is conquered Involvement of the auditory nerve is apt to lead to permanent deafness, which may appear during the course of the disease or not until a month or two later Mental impairment following epidemic meningitis is rare

A significant number of patients, even when treated with effective antibiotics, *develop subdural collections of fluid*, which may be unilateral or bilateral The fluid is usually sterile, it is xanthochromic or bloody, and its protein content is extremely high. Subdural fluid collections are most often found in infants under 2 years of age, they are similar to those of traumatic origin and the membrane which encloses them is quite similar Such fluid collections appear to be the result of injury to cerebral cells and blood vessels The presence of a subdural collection should be suspected in any patient whose clinical course is not one of rapidly progressing return toward normal Thus, the appearance of signs of increasing intracranial pressure, palsy of an extremity, a convulsion, vomiting and persisting fever should bring this condition to mind, and warrants bilateral subdural taps in an infant whose anterior fontanelle is open In older children a more formidable procedure—that of making burr holes in the skull—is required, but when there is a strong suspicion that a subdural collection is present, this procedure is necessary

few days, at the end of which time the temperature has fallen to nearly normal levels and the infection has been conquered A period of general weakness, headache, and intolerance for sunlight, may then intervene, followed by complete recovery. When serum was the only specific therapy available, some of the cases failed to clear up, and suffered a recurrence of the disease, others became chronic, and long-drawn out. Of these chronic cases, formerly not unusual, but now seldom seen, some were due to obstruction of the circulation of the spinal fluid at the foramina of Magendie and Luschka, with resulting accumulation of fluid in the lateral ventricles and the formation of an internal hydrocephalus Such cases lasted for several months and were apt to show extreme emaciation and steady deterioration before the practically inevitable death. Another type of chronic infection consisted of the development of a localized process at the base of the brain—a posterior basilar meningitis In these cases, the symptoms were somewhat similar to those of the other chronic form without the evidences of increasing intracranial pressure

THE COMPLICATIONS AND SEQUELÆ OF MENINGOCOCCUS MENINGITIS

Since the advent of chemotherapy, all complications and sequelæ are comparatively unusual The earlier treatment is instituted, the less likely are they to occur Those described on the following paragraphs were common in the days prior to its general use

Those Involving the Central Nervous System, and Due to Infection of the Meninges and Cranial Nerves.—Hydrocephalus may be due to blocking off of the spinal fluid at the outlet of the ventricles, causing an internal hydrocephalus, or it may be due to a diminution in the rate of absorption of the spinal fluid probably due in turn to a contraction in the size of the absorption area in the subarachnoid space, resulting from adhesions. If the adhesions are in the spinal column

meningitis do not exhibit a purpuric rash, and in some instances only very few petechiæ are present. Therefore, the identification of the specific bacterium causing the meningitis must in every instance be made by laboratory means. In the vast majority of cases of purulent meningitis which have been untreated before the spinal fluid is obtained, the causative organism can be identified within 10 to 20 minutes by direct examination of the spinal fluid Maximum effort should be expended on this examination because a rapid and accurate bacteriologic identification enables the physician to begin promptly the most effective type of chemotherapy, it is upon prompt and effective treatment that a completely satisfactory outcome depends Direct examination of the spinal fluid is therefore to be regarded as the first step in proper therapy Culture of the spinal fluid and blood are important confirmatory aids, but they do not yield information in time to be of primary importance as a guide to treatment Sometimes a stain of a smear of material obtained by puncturing one or more petechiæ may reveal Gram-negative organisms with the morphologic appearance of Neisseria Beginning about two weeks after infection, the diagnosis may be verified by agglutination with the patient's blood serum

The Spinal Fluid.—The spinal fluid circulates both in the ventricles and around the brain and spinal cord. It is apparently derived from two sources, first and principally, from the choroid plexus of the cerebral ventricles, which in turn derives the fluid from the blood by a process of filtration and secretion, and second, from the perivascular systems of the nerve tissues

From each lateral ventricle the fluid passes through the foramen of Monro into the third ventricle, and thence by the aqueduct of Sylvius into the fourth ventricle. From there the cerebrospinal fluid passes through the foramina of Magendie and Luschka into the cistern below the cerebellum, whence it passes downward along the arachnoid spaces of the spinal canal, and upward around the brain The fluid apparently returns to the general circulation by a process

The part which subdural collections play in the neurologic sequelæ which may follow meningitis is not certain Some of these collections certainly go unrecognized, and absorption occurs spontaneously without permanent injury to the brain Similarly, complete healing occurs when the fluid is entirely withdrawn In some patients the fluid persists unless the surrounding membrane is removed surgically. It is possible that untreated collections of this sort may cause permanent compression injury to the brain

Complications Not Related to the Central Nervous System, but Due Rather to the Blood Stream Infection and Toxemia or to a Secondary Infection.—Pneumonia formerly occurred fairly frequently, particularly as a terminal infection in the patients dying after the first few days In young children otitis media is still a common complication Infection of the heart was fairly common in the septicemic type of the disease, and involved either the pericardium or the endocardium. Myocarditis was also frequently found in some epidemics.

A distressing polyarthritis is still not uncommon in the early stages of meningococcic infections, but is transitory and clears up with the hemorrhagic rash A monoarthritis especially of the knee and accompanied by a purulent exudate containing meningococci, may appear later in the illness, is not notably painful, and eventually clears up entirely A peripheral thrombophlebitis is not unusual among adult patients

THE DIAGNOSIS OF MENINGOCOCCUS MENINGITIS

The diagnosis of meningococcic meningitis can be made on clinical grounds with a high degree of certainty in typical cases, in which clear signs of meningitis are combined with a purpuric eruption This is possible because other bacteria which commonly cause meningitis (as H influenzæ) very rarely produce purpura. The presence of a known outbreak of meningococcic infection in the community also adds the certainty of the specific diagnosis in a given case. It must be emphasized, however, that many cases of meningococcic

TABLE 11 —CHARACTERISTICS OF THE SPINAL FLUIDS IN VARIOUS CONDITIONS

Meningeal condition	*Amount, cc*	*Appearance*	*Cytology*	*Bacteriology*	*Albumin*	*Globulin*	*Sugar*
Normal	5-10	Clear	5-10 cells Mononuclears	Negative by smear and culture	±	±	Normal
Meningismus	20-50	Clear	5 10 cells (occasionally more) mononuclears	Negative by smear and culture	± to +	± to +	Normal
Poliomyelitis and encephalitis	15-35	Clear or sl hazy fibrin web may form	15 1000 Mononuclears usually predominate, polynucleosis common early	Negative by smear and culture	+ to ++	+ to ++	Normal or high
Tuberculous *meningitis*	20-50	Clear to hazy, fibrin web	50 300 *Usually* mononucleosis, rarely polynucleosis	Tubercle bacilli by smear, culture and guinea-pig inoculation	+ to +++	+ to +++	Rarely normal; *usually* decreased
Serous meningitis	15-35	Hazy to cloudy	Up to 1000 or more, usually polynucleosis	Negative by smear and culture	+ to ++	+ to ++	Normal
Purulent meningitis	20 60	Hazy to purulent	Indefinitely high polynucleosis	Infecting organism by smear and culture	+ to ++++	+ to ++++	May be normal at onset, decreases rapidly as disease advances

Every spinal fluid should be completely examined Diagnosis in meningitis made on result of direct examination of spinal fluid if possible and confirmed by culture Smears from cloudy or hazy fluids always stained by Gram method When organisms are seen on smears which morphologically resemble meningococci, H influenzae, or pneumococci, a capsular swelling test with specific serum should be carried out in order to make an immediate identification of the positive organism if possible. Cultures should be made on various media as described in the text All cultures isolated should be thoroughly studied and classified The return to normal of the spinal fluid sugar in meningitis is a favorable prognostic sign

of filtration into the cerebral sinuses, and also by a drainage of fluid into the lymphatics. The normal amount of fluid is probably from 100 to 200 ml

The normal spinal fluid is perfectly clear, like water. There are less than 10 white blood cells per cubic millimeter. The specific gravity averages 1 005 with a normal range of 1.003 to 1 010. Protein, which in the normal fluid is nearly all globulin, *may range from 10 to 25 milligrams per 100 ml. of* fluid with an average of 20. Glucose is present in concentration of 50 to 75 mg per 100 ml When 0 05 ml. or more of normal spinal fluid is boiled with 1 0 ml. of Benedict's solution, a positive reaction occurs Lactic acid is less than 20 to 25 mg per ml and chlorides average 700 mg per 100 ml or slightly more than in the blood When the pressure of spinal fluid is normal, the rate of flow through an average needle of 15-gauge is 10 to 15 drops a minute with the patient in a horizontal position By the Ayer spinal fluid manometer, with the patient in the horizontal position, the pressure is normally 80–135 mm of water.

In the septicemic type of meningococcus infection, the spinal fluid may appear perfectly normal, particularly early in the disease. In meningococcus infections of the meninges, however, the spinal fluid is under increased pressure and the fluid is usually quite cloudy in appearance because of the presence of a very large increase in leukocytes. Cell counts made on fluids that have been allowed to stand more than a few minutes may be quite inaccurate on account of clotting and clumping. The protein content is increased, and Pandy's test, indicating the presence of an abnormal amount of globulin, is positive. Sugar is usually absent or greatly reduced, and its return to the spinal fluid is of good prognostic significance. Chlorides are reduced as in the blood but the lactic acid content of the spinal fluid is increased in meningitis although in the blood it remains at a normal or low level. Smears usually show *Gram-negative diplococci, of which* some may be intracellular. In general the higher in the cerebrospinal fluid pool one explores, *i.e.*, lumbar region, cistern

media especially designed to favor the growth of the tubercle bacillus, and guinea pig inoculations are made.

A second tube, unopened, is placed in the incubator in ordinary atmosphere at 37° C. It is examined for growth of bacteria after 8, 12, 24, and 48 hours. Occasionally this tube of spinal fluid proves to be the best culture media showing growth of meningococci when artificial media fail to do so.

A third tube of spinal fluid is set aside for possible use in virologic studies if this is deemed necessary (i.e., for inoculation of animals and tissue culture media).

2. *Preparation and Examination of Smears.*—The remaining, or fourth, tube of spinal fluid is centrifuged for 15 minutes at 2500 rpm (if the presence of tubercle bacilli is suspected, the tube is centrifuged for 30 minutes). The supernatant fluid is then decanted and used for chemical estimation of sugar, protein, and chloride. The sediment is taken up with a sterile capillary pipette and two drops are placed one upon the other (for further concentration) in the center of each of three slides. After drying in air, one of the slides is stained with Gram-stain and the others are saved for future reference (for example, if it later appears to be required, acid-fast stains for tubercle bacilli can be made). The Gram-stained slide is searched carefully with an oil immersion microscope lens for the presence of bacteria. If Gram-negative organisms morphologically resembling the Neisseria group are seen, an attempt is made to make a specific etiologic diagnosis by means of the capsular swelling reaction (Quellung) with type specific anti-meningococcic serum. This is done in the following manner: A loopful of the spinal fluid sediment is placed on a clean cover slip and a loopful of type 1 anti-meningococcus serum is added, together with ¼ of a loopful of methylene blue. The cover slip is then inverted upon the slide. A similar preparation is made using type 2 alpha serum. These slides are then carefully examined under the oil immersion lens for the presence of capsular swelling of the organisms. If such swelling is observed in

and lateral ventricles, the more meningococci and the fewer pus cells are found in the fluid. Cultures of the spinal fluid are usually positive early in the disease, but a growth is difficult to obtain when the organisms cannot be found on smears. Twenty-four hours after the start of adequate sulfadiazine therapy the spinal fluid usually shows evidence of improvement. This is indicated by an increase in sugar concentration, absence of bacteria or great reduction in their numbers in smears, and a sterile culture. In this period there may be a decrease in the total number of cells, with a fall in the percentage of polymorphonuclears. As improvement continues, organisms disappear entirely from smears and culture; sugar concentration returns to normal, protein content falls, and the total number of white cells decreases greatly, with most of the remaining cells being monocytic.

Technic of Spinal Fluid Examination.—Bacteriologic examination of the spinal fluid should be carried out as rapidly as possible after the fluid is obtained. It is essential that the services of a competent bacteriologist be available at all times in order to obtain the best results. Under aseptic conditions, the spinal fluid is collected in approximately 3 ml quantities into each of four sterile, chemically clean test tubes, which are stoppered with cotton plugs.

1. *Technic Used to Culture Spinal Fluid.*—Cultures should be planted as soon as possible after the spinal fluid is obtained. One of the four tubes of spinal fluid is used for culturing, the following media being heavily inoculated by means of a sterile pipette: 1 blood agar plate, 1 tube of blood broth containing 1 per cent penicillinase, 1 Levinthal agar plate, 1 tube of Levinthal broth, 1 Endo agar plate, and 1 tube of Brewer's thioglycollate broth. The blood agar plate and the tube of blood broth are incubated at 37° C. in a jar containing 10 per cent carbon dioxide. The remaining media, together with an unopened tube of spinal fluid are incubated at 37° C. in ordinary atmosphere. When tuberculous meningitis is suspected, the spinal fluid is cultured on

TABLE 12.—SEMI-QUANTITATIVE TEST FOR ESTIMATING SUGAR CONTENT OF SPINAL FLUID[1]

Tube Number (Each contains 1.0 ml Benedict's)	*Spinal Fluid, ml*	*Reduction of Benedict's Solution*					
1	0.05	+	0	0	0	0	0
2	0.10	+	+	0	0	0	0
3	0.15	+	+	+	0	0	0
4	0.20	+	+	+	+	0	0
5	0.25	+	+	+	+	+	0
6	0.00	0	0	0	0	0	
Milligrams of Sugar per 100 ml		>50	40-50	30-40	20-30	10-20	<15

[1] From Holt Pediatrics, Holt, L. E., Jr., and McIntosh, R., Appleton-Century-Crofts, Inc., Twelfth Edition, New York, 1953 (page 1203).

THE DIFFERENTIAL DIAGNOSIS OF MENINGOCOCCUS MENINGITIS

Conditions With True Involvement of the Meninges

1. *Meningitis Due to Other Pyogenic Organisms.*—When typical signs of meningeal irritation are present the diagnosis of meningitis is not difficult. When such symptoms are accompanied by a purpuric rash the diagnosis of meningococcic meningitis is very nearly always correct. However, only by specific bacteriologic identification can the diagnosis be made with absolute certainty. Meningitis due to H. influenzæ, pneumococci, streptococci and members of the enteric group of organisms can be definitely differentiated from meningococcic meningitis only in this way. In all these forms of meningitis the generalized symptoms of septicemia may be followed by evidences of meningitis. This is particularly true of H. influenzæ meningitis, and it is very frequently the case with the other organisms listed. However, pneumococci and streptococci may spread to the meninges after having caused an infection in neighboring tissues, such as the middle ear, the mastoid bone, and the paranasal sinuses, and the presence of such foci are against the meningococcus as the causative organism.

the preparation containing type 1 serum, one can be practically certain that the organism is a type 1 meningococcus; a similar finding in the type 2 alpha serum means that the causative organism is a meningococcus of the type 2 alpha group. It should be noted that the absence of capsular swelling on both slides does not exclude the presence of the type 2 meningococcus since this organism is not encapsulated and does not give a Quellung reaction

If the pleomorphic Gram-negative rods or coccobacilli are seen instead of Gram-negative diplococci on the dried, stained smear, Quellung reaction tests should be set up using type a and type b H influenzæ sera. If Gram-positive diplococci or Gram-positive cocci in short chains are seen on the smear, Quellung reactions with anti-pneumococcus sera should be set up

3 *Chemical Examination of the Spinal Fluid* —Of very *great importance in the diagnosis and treatment of meningitis* is the estimation of the concentration of sugar in the spinal fluid The following semiquantitative method is extremely useful

One ml of Benedict's qualitative solution is placed in each of six chemically clean test tubes, and numbered 1 through 6 0.05 ml of the decanted spinal fluid supernate referred to in the preceding section is added to tube number one, 0 10 ml. is added to tube number two, 0 15 ml is added to tube number three, 0.20 ml is added to tube number four, and 0 25 ml is added to tube number five No spinal fluid is added to tube number six which serves as a control The tubes are thoroughly shaken and placed in a boiling water bath for ten minutes At the end of this time the tubes are read, a green to yellow color as compared with the blue control is evidence of reduction of the Benedict's solution. In normal spinal fluid, tubes five, four, three, and two are positive; this corresponds to a concentration of sugar of 40 to 50 mgm per 100 ml. of spinal fluid The following table shows the pattern obtained with various concentrations of spinal fluid sugar.

TABLE 12.—SEMI-QUANTITATIVE TEST FOR ESTIMATING SUGAR CONTENT OF SPINAL FLUID[1]

Tube Number (Each contains 1.0 ml Benedict's)	*Spinal Fluid, ml*	*Reduction of Benedict's Solution*					
1	0.05	+	0	0	0	0	0
2	0.10	+	+	0	0	0	0
3	0.15	+	+	+	0	0	0
4	0.20	+	+	+	+	0	0
5	0.25	+	+	+	+	+	0
6	0.00	0	0	0	0	0	
Milligrams of Sugar per 100 ml		>50	40-50	30-40	20-30	10-20	<15

[1] From Holt Pediatrics, Holt, L. E., Jr., and McIntosh, R. Appleton-Century-Crofts, Inc., Twelfth Edition. New York, 1953 (page 1203).

THE DIFFERENTIAL DIAGNOSIS OF MENINGOCOCCUS MENINGITIS

Conditions With True Involvement of the Meninges

1. *Meningitis Due to Other Pyogenic Organisms.*—When typical signs of meningeal irritation are present the diagnosis of meningitis is not difficult. When such symptoms are accompanied by a purpuric rash the diagnosis of meningococcic meningitis is very nearly always correct. However, only by specific bacteriologic identification can the diagnosis be made with absolute certainty. Meningitis due to H. influenzæ, pneumococci, streptococci and members of the enteric group of organisms can be definitely differentiated from meningococcic meningitis only in this way. In all these forms of meningitis the generalized symptoms of septicemia may be followed by evidences of meningitis. This is particularly true of H. influenzæ meningitis, and it is very frequently the case with the other organisms listed. However, pneumococci and streptococci may spread to the meninges after having caused an infection in neighboring tissues, such as the middle ear, the mastoid bone, and the paranasal sinuses, and the presence of such foci are against the meningococcus as the causative organism.

Great difficulty arises in making an exact bacteriologic diagnosis in those cases in which antimicrobial therapy has been given before the spinal fluid is available for examination In these instances no organisms may be present on smear and none may be obtained on culture. The assumption must not be made that the meningococcus is the causative organism unless a typical purpuric eruption is present. It is much safer to assume that H influenzæ and a pneumococcus are responsible for the meningitis, and to choose the antibiotic therapy which is best suited for treating these infections (see treatment of meningitis of undetermined origin, page 434).

Serous meningitis is due to some infection outside, but near the dura, which causes irritation of the meninges and the clinical findings of meningitis except that there is an absence of organisms in the spinal fluid.

2. *Tuberculous Meningitis.*—This type of meningitis is customarily less abrupt in onset than meningococcus and other forms of purulent meningitis. The spinal fluid in tuberculous meningitis is usually clear or only hazy and contains 50 to 350 cells per cubic millimeter in contrast with the cloudy spinal fluid and the high cell count of meningococcic meningitis. Nearly always lymphocytes predominate in the spinal fluid in tuberculous meningitis, while polymorphonuclears comprise the vast majority of the cells in meningococcic meningitis. Careful examination of acid-fast stains of smears of the sediment of centrifuged spinal fluid reveals the presence of tubercule bacilli in a high percentage of cases of tuberculous meningitis, and culture on special media and guinea pig inoculation eventually make the diagnosis certain In addition there is frequently a history of exposure to tuberculosis, and physical and roentgen examination of the chest very often reveal evidences of miliary tuberculosis, caseous pneumonia, or tuberculous lymph nodes In the majority of cases the intradermal tuberculin test is strongly positive, although it may be negative at the beginning of the disease or in extremely ill patients. There is generally, therefore, no difficulty in distinguishing between tuberculous and

meningococcic meningitis. However, the differentiation between partially treated meningococcic meningitis and early tuberculous meningitis may be extremely difficult since the causative organisms may not be demonstrable in the spinal fluid In such cases all the collateral evidence must be weighed carefully, and a decision reached quickly since early treatment is essential in both conditions. On several occasions we have been obliged to begin antibiotic treatment for both purulent and tuberculous meningitis, because previous chemotherapy had rendered unreliable the bacteriologic examination of the spinal fluid

3 *Poliomyelitis* —This disease in the non-paralytic form may show symptoms of meningeal irritation strongly suggestive of a meningitis Hyperesthesia is apt to be more marked in infantile paralysis, and the knee reflexes may be unequally increased early or unequally decreased later, while in meningitis the reflexes are usually equally hyperactive In both diseases spasm of the muscles of the neck, spine, and hamstrings causes stiffness of the neck and back and positive Kernig's signs, but in poliomyelitis spasm will be found in other groups of muscles not involved in meningitis

The spinal fluid usually aids materially in the differentiation. In poliomyelitis, it has no more cloudiness than a ground-glass appearance, the cells vary from 30 to 200 or 300, or in rare cases up to 1000, and they are often mostly mononuclear Sugar is normal or increased in amount, and albumin is not greatly increased Of most importance, the fluid is sterile. In some laboratories tissue culture technics are available which make possible isolation of the polio virus from the stool, and demonstrate the development of specific anti-polio antibodies in the serum

Conditions Without True Involvement of the Meninges.—1 Meningismus is a condition which is characterized by symptoms of meningeal involvement appearing in the course of some other disease, but in which the spinal fluid, while markedly increased in quantity and thus in pressure, nevertheless is usually entirely normal in character and is always

negative on bacteriological examination. This symptom-complex may occur with a great number of different diseases, but most of the cases occur with pneumonia, influenza, or whooping cough and similar infections, and in gastro-enteritis in children. Even marked symptoms of meningeal irritation may be found, but great relief is usually obtained by lessening the pressure of the spinal fluid by lumbar puncture.

2. *Tetanus, typhoid fever, and typhus fever* may at times offer perplexing similarities to meningitis, and such localized conditions as a brain abscess and a brain tumor must also be considered.

THE MORTALITY AND PROGNOSIS OF MENINGOCOCCUS MENINGITIS

Before the introduction of the antimeningococcus serum in 1907–1908, the mortality-rate in epidemic meningitis varied from 50 to 90 per cent, depending on the type of epidemic. The use of the serum then cut the death-rate down to a variable figure between 20 and 50 per cent, lower in endemic than epidemic cases, but the mortality in the fulminating and septicemic types of cases remained very high, and infants under one year of age continued to show a general mortality approximating 50 per cent. However, the use of sulfadiazine has cut the mortality rate to a very low point in properly treated cases, in fact, deaths resulting from meningococcus meningitis treated with this drug are now almost entirely encountered among patients with the Waterhouse-Friderichsen form of the disease, or among those in whom a correct diagnosis and proper treatment have been long delayed.

Thus, the prognosis is now generally excellent, but besides the use of the drug several factors may have significance. The type of infection and also the resistance of the individual are of importance. Age formerly was significant, the outlook having been more serious in adults and infants than in school children. Even now the difficulty in making the diagnosis

in infants prevents the attainment of the best possible results in this age group Cases early in epidemics were apt to have a less favorable outlook than sporadic cases. Of good omen are a decrease in the leukocytosis, an increase in the sugar content of the spinal fluid, and the disappearance of meningococci from the spinal fluid

Symptoms and signs of grave prognosis include delirium, coma, convulsions, marked skin hemorrhages, a fall in blood pressure, signs of shock and circulatory collapse, a high eosinophile count in the circulating blood, and also the presence of pneumonia or endocarditis, and the development of hydrocephalus Most patients who recover, recover completely, although some headache or emotional instability may persist for a number of weeks Happily, such sequelæ as nerve deafness and hydrocephalus are now very rare Loss of mental capacity seems to be rare in meningococcic meningitis as compared with H influenzæ and pneumococcic meningitis, and the same is true of convulsive disorders. And finally, of very great importance in the outcome of the case are the promptness and persistence with which chemotherapy is administered

ISOLATION, QUARANTINE, AND PROPHYLAXIS IN MENINGOCOCCIC MENINGITIS

Epidemic meningitis is probably more frequently contracted from exposure to a healthy carrier than to a case of the disease Carriers are at times very numerous in a general population, and contact with them can hardly be avoided Patients should be isolated, and every effort made to restrict contamination of others with the discharges from the nose and throat

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isolation of the patient is not required after this period Contacts of a meningitis patient are not quarantined, and

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should be isolated and given sulfadiazine in dosage of 2 to 4 grams daily for two days, after which isolation may be discontinued. The prophylactic use of sulfadiazine is the chief resource for clearing up carriers of meningococci.

THE TREATMENT OF MENINGOCOCCIC MENINGITIS

Only the prompt recognition of clinical signs of early meningitis together with quick bacteriologic identification of the meningococcus can bring about the optimal therapeutic results. Sulfadiazine is the drug of choice, but many authorities give penicillin in addition. Antimeningococcus serum is no longer used, since the best results obtained with it rarely bettered a case fatality rate of 20 per cent, while with modern antimicrobial therapy the case fatality rate is under 5 per cent The occurrence of serum sickness, and the higher rate of complications and sequelæ among serum treated cases have also contributed to the abandonment of this form of therapy.

1 **Sulfadiazine Therapy.**—Blood for culture is obtained and lumbar puncture is performed as soon as possible after the clinical diagnosis of meningitis (or possible meningitis) is made An intravenous drip of 0 45 per cent sodium chloride in 2 5 per cent dextrose solution is established as soon as the diagnosis is confirmed by the finding of cloudy spinal fluid While the fluid is being examined in the laboratory a 5 per cent solution of sodium sulfadiazine is given intravenously, the injection being made into the lower end of the tubing of the intravenous set, with a clamp occluding the tubing above the point of injection The dose of sodium sulfadiazine for this first infusion is 50 mg per kilogram of body weight, at least ten minutes are used in making the injection There is no reason to await the rseult of the examination of the smears of the spinal fluid before instituting this form of treatment, since we employ sulfadiazine with other drugs in the treatment of all types of meningitis except those caused by the Enterobacteriaceæ (Salmonella,

they are not excluded from school However, family contacts, schoolmates, and barracks mates of a meningococcic meningitis patient should be given sulfadiazine as prophylaxis, since in our experience, about 10 per cent of cases are secondary ones One gram of sulfadiazine twice daily for one week is recommended for adults, children should receive half this dose

The spread of meningitis is greatly favored by crowding and inadequate housing facilities. Thus, the case incidence rate is greatest among the lowest economic groups in civilian life, and in crowded army and navy barracks

CARRIERS OF MENINGOCOCCI

For the detection of carriers the upper posterior wall of the pharynx is swabbed by using a cotton swab on the end of a wire or applicator bent at an angle to reach behind the soft palate Plates, preferably of vitamin agar, are inoculated at one point near the circumference and then by means of a platinum loop a number of streaks radiating from this point are made on the surface At the end of twenty-four hours characteristic colonies are fished and tested by slide agglutination against normal serum and antimeningitis serum. A Gram-stain is then done on the test slide. Other Gram-negative cocci are ruled out by the agglutination tests, also by sugar fermentation tests, while a Gram-positive coccus and two Gram-negative bacilli which occur in the nasopharynx and give a definite agglutination, are ruled out by a study of the stained slides This method, as used by the Research Laboratory of the New York City Department of Health, enables a report to be given at the end of twenty-four hours.

The number of carriers developing from cases treated with sulfonamides or penicillin is very small. In the presence of an epidemic in a military group or school, however, the carrier problem assumes considerable importance. Then carriers should be carefully sought and if id

It is important to bear in mind certain other clinical manifestations of sulfadiazine toxicity and hypersensitivity. These include fever, various forms of eruption, and symptoms of involvement of the central nervous system. Fever due to the drug may develop twenty-four to forty-eight hours after the start of chemotherapy. This is often interpreted to mean that the infection is not under control, but the other manifestations of meningitis and the spinal fluid findings will be found to be improving and often will continue to improve even if the drug is stopped. Fever developing after the temperature has once returned to normal may be due to a complication of the infection but it may also be due to the chemotherapy.

Peripheral motor neuritis may be caused by the sulfonamide, and usually disappears promptly when the drug is stopped. Cases developing encephalopathy even with permanent mental damage have also been described.

2. **Penicillin Therapy.**—Most authors believe that penicillin should be used in addition to sulfadiazine for severely ill patients, we recommend its use for one or two days in all cases. Procaine penicillin is used in dosage ranging from 300,000 units twice daily for infants to 600,000 to 1,000,000 units twice daily for older children and adults.

3. **Duration of Chemotherapy.**—In nearly every case five days of sulfadiazine therapy is sufficient and chemotherapy may be stopped at this time. However, this is only done when it is clear that the patient's clinical course has been satisfactory, and his spinal fluid has returned essentially to normal. When the course is satisfactory the patient's mental state is normal or nearly so by the second or third day of therapy, his temperature is at a lower level (not necessarily normal), and signs of meningeal irritation are definitely less marked. At this time the spinal fluid contains fewer cells, and the concentration of sugar approaches normal values, no bacteria are seen on smears, and cultures are sterile. By the fifth day the temperature is normal or nearly so in most cases, no signs of increased intracranial pressure are present,

E coli, etc). After the initial dose, the sulfadiazine is given by mouth if there is no vomiting The oral dose of sulfadiazine is 200 mg per kilogram of body weight per day for infants and small children, and 100 mg. per kilogram for older children and adults These quantities are divided into 4 to 6 doses daily A total daily dose of six grams should not be exceeded regardless of the patient's weight

Subsequently, if sulfadiazine cannot be given by mouth because the patient is comatose, it may be administered through a plastic tube passed through the nose into the stomach, or sodium sulfadiazine may be given by intravenous or subcutaneous injection. The latter routes must be used when vomiting is present. The total daily intravenous dose of sodium sulfadiazine (excluding the initial injection) for infants and young children is 150 mg per kilogram of body weight per day (divided into 3 doses of 50 mg per kilogram each) For older children the total daily dose of sodium sulfadiazine injected intravenously is 100 mg per kilogram For all these intravenous injections this curative chemical is given in a 5 per cent solution

Sodium sulfadiazine may also be used subcutaneously, in a 1 per cent solution, in the same total dosage, as that employed for intravenous injection, but only two doses daily, at twelve-hour intervals are given by this route.

Sulfadiazine therapy is usually continued for a total of five days It is wise to estimate the blood concentration of sulfadiazine 24 hours and 48 hours after beginning sulfadiazine therapy. This may be done by simple micro-methods which employ blood obtained by pricking the finger The estimation should be made mid-way between administration of two doses A drug level of 8 to 10 mg per 100 ml. of blood should be maintained A concentration higher than this is not necessary, and increases the risk of kidney damage. The dosage should be adjusted accordingly. The fluid intake of the patient should be maintained at an adequate level, this is of importance in minimizing the risk of renal injury due to sulfadiazine

meter also require immediate institution of such therapy, even when clinical signs of shock are not present. For replacement therapy we have employed cortisone exclusively, although it is very probable that meticorten is also effective Aqueous adrenal cortical extract is ineffective because it contains only 0.1 mg of cortisone per ml

The first two doses of cortisone should be given intravenously, the remaining doses intravenously or by mouth, depending on the patient's condition. The following dosage schedule is given as a rough guide to cortisone therapy, but this schedule should be altered in accordance with the clinical and laboratory findings Infants and children less than two years old should be given 50 mg of cortisone intravenously and 25 mg by mouth as soon as cortisone therapy is decided upon If the patient's general condition improves, if blood pressure levels rise, and if a circulating eosinophile count taken two hours after the initial cortisone injection shows an appreciable fall (50 per cent or more), no more cortisone is given intravenously Cortisone therapy is then continued, giving 25 mg by mouth every four hours for the next two days If signs of improvement are not noted within two hours after the first intravenous injection of cortisone, a second dose of the same size is given by this route Children two to eight years old are given doses 50 to 100 per cent larger than those prescribed for children under two years of age Adolescents and adults are given two to three times the infant dosage of cortisone Figure 57 shows the effect of cortisone upon blood pressure and eosinophile count of a patient with fulminating meningococcemia and early meningitis

This patient, a girl of eight years, was admitted to the hospital with an extensive hemorrhagic eruption, low blood pressure, and lethargy Fourteen hours after admission, despite plasma and blood transfusions, and intensive chemotherapy, she became comatose and showed signs of circulatory collapse At this time her blood eosinophile count was found to be 75 per cubic millimeter (rather than the expected

also no symptoms of a progressing central nervous lesion (subdural collection of fluid) and the appetite is good. Smears and cultures of the spinal fluid are negative for bacteria, its sugar content is normal, and fewer than 100 cells per cubic millimeter are present (nearly all lymphocytes)

4. **Treatment of Circulatory Collapse, and Shock** (Waterhouse-Friderichsen Syndrome) —Some patients enter the hospital exhibiting obvious signs of circulatory collapse In other instances, a period in which the circulatory apparatus appears to be functioning well is followed by sudden appearance of pallor, fall in blood pressure, and shock. It is probable that these symptoms are due, at least in part, to injury of the adrenal gland, and decrease of production of the 11-oxygenated corticosteroids such as cortisone and compound F It is sometimes possible to predict the occurrence of circulatory collapse by demonstrating a progressive fall in blood pressure which sometimes precedes this state In other instances the onset of shock is so sudden that serial blood pressure readings are of little prognostic value We have found, however, that the blood eosinophile count is usually a useful clinical guide to the state of adrenal cortical function. A decrease of the blood eosinophile count is a characteristic part of the "alarm" reaction which takes place during acute infections of moderate or serious infection When the adrenal cortex is functioning properly during an acute infection, the blood eosinophile count lies between 0 and 25 per cubic millimeter, instead of the normal range of 100 to 200. When the adrenal cortex has been injured (as in the Waterhouse-Friderichsen syndrome) the circulating eosinophile count may be in the normal range, rather than 0 to 25 Thus a high eosinophile count in the early, untreated stage of meningococcemia or meningococcic meningitis should be regarded as evidence of adrenal cortical injury

The presence of circulatory collapse and of other signs of Waterhouse-Friderichsen syndrome requires replacement of 11-oxygenated corticosteroids. A progressively falling blood pressure or an eosinophile count above 25 per cubic milli-

Experience has shown, however, that no enhancement of the infection has been found with cortisone therapy, probably because the effectiveness of sulfadiazine against the meningococcus prevents such an occurrence. The suggestion has also been made that it might be advantageous to administer cortisone to all patients with meningococcic infection, since the onset of circulatory failure and shock may be sudden and unexpected We do not believe cortisone should be employed in every case, but its use in severe meningococcic infections, even when laboratory and clinical evidence of injury of the adrenal cortex is lacking, seems to be worth an extensive trial

In addition to cortisone, other measures aimed at raising the blood pressure should be used when shock is present or appears to be imminent. The most useful of these is the intravenous administration of nor-epinephrine by constant intravenous drip Blood and plasma transfusions also have a place in the therapy of the Waterhouse-Friderichsen syndrome, but their beneficial effect upon the blood pressure is usually only temporary. When gallop rhythm, cardiac enlargement and electrocardiographic abnormalities indicate serious myocardial damage and strain, digitalization should be considered Here the same principles apply as those which have been described in detail in the section on Diphtheritic Myocarditis (page 140)

5. **General Treatment.**—As in the treatment for every severe infection, fluid and electrolyte balance should be maintained Usually this is best accomplished by continuous intravenous therapy, which should be instituted on admission in all except the most benign cases Extreme restlessness, violent headache, delirium, and mania should be controlled by such sedatives as paraldehyde and chloral hydrate given by rectum It is generally believed that morphine should not be administered to meningitis patients Convulsions should be treated in the same way, or intravenous injection of sodium phenobarbital or inhalation of chloroform may be used. Fever of extreme degree should be treated with tepid water

0 to 25), and cortisone treatment was started as indicated by the arrows on Figure 57 The first two doses of the drug were given intravenously, the last three by mouth. Within a few hours after initiation of cortisone therapy the eosinophile count had fallen to 25, and in ten to twelve hours the

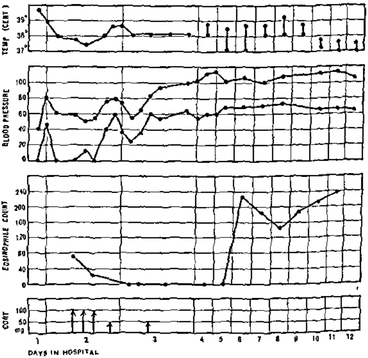


FIG. 57 —Fulminating meningococcemia treated with cortisone and sulfadiazine

blood pressure began to rise and continued to do so. Within 36 hours the patient was greatly improved and she eventually made a complete recovery. There is little doubt that this child would have succumbed without hormone therapy.

Objection has been made to the use of cortisone in the treatment of meningococcic infections on the grounds that the drug tends to favor the spread of an infectious process.

to those found in some types of H. influenzæ For example, H. influenzæ, type b, and some type 6 pneumococci share a common antigen.

Pathogenesis of H. Influenzæ Meningitis.—H influenzæ type b causes the vast majority of cases of influenza bacillus meningitis. The organism readily establishes itself on the mucosa of the upper respiratory tract of the susceptible individual, causing nasopharyngitis, fever, and other constitutional symptoms. Usually, the disease does not progress beyond this, and spontaneous recovery with the production of immunity follows In some cases, however, the infection spreads to the epiglottis, trachea, bronchi, lungs, and middle ear, and by extension from the ear, the meninges may become infected. More commonly, invasion of the blood directly from the nasopharynx occurs, and septicemia and meningitis may then follow.

Over 80 per cent of the cases of H influenzæ meningitis occur in children three months to three years of age Older children are much less often affected, and adult cases are rare Fothergill and Wright showed that immunity to H influenzæ meningitis was correlated with the bactericidal power of the blood The blood of children in the three-month to three-year age group has very little bactericidal action against H influenzæ, the blood of older persons (who rarely suffer from influenza bacillus meningitis) exhibits a high degree of bactericidal power In the immune individual, bactericidal effect of the blood is due to lysis of the organism, and to phagocytosis The specific antibody responsible for these effects appears to combine with and to neutralize the specific capsular polysaccharide

Symptoms of H Influenzæ Meningitis.—The disease may begin suddenly with well marked evidences of meningitis from the onset More often however, onset is much more gradual and symptoms of meningitis may appear only after a number of days of a respiratory infection of mild or only moderate severity. A sudden, explosive onset is much less common in this type of meningitis than it is when the meningo-

or alcohol sponges. A cool oxygen tent is often very quieting for delirious patients, and seems to improve the general condition and perhaps their circulatory status Good nursing care contributes greatly to the patient's comfort. Constant observation by a competent nurse and physician, and continual re-evaluation of the patient's condition are essential

II. HEMOPHILUS INFLUENZÆ MENINGITIS

H influenzæ is the most common cause of bacterial meningitis among infants and children at the present time. The great majority of cases of H influenzæ meningitis are caused by encapsulated forms of this organism, although rough variant (unencapsulated) strains may rarely be responsible.

Bacteriology.—H. influenzæ is a Gram-negative, nonmotile, ærobic bacillus. Morphologically it exhibits considerable pleomorphism In spinal fluid it occurs mainly as a coccobacillus. In this form H influenzæ organisms may resemble diplococci, and if the Gram-stain has been improperly made, they may be considered to be pneumococci by an inexperienced observer However, at least a few definite forms can be found in every preparation, and in these a polar, pale-stained granule may be seen

Like other members of the genus Hemophilus, H influenzæ possesses only poorly developed enzyme mechanisms, and requires an enriched medium for its isolation and cultivation Two growth factors, designated the X and V factors, which are present in mammalian blood, are necessary for multiplication of the organism

Strains of H influenzæ isolated from spinal fluid in cases of meningitis are practically always encapsulated. Encapsulated members of the H influenzæ species are divisible into six types, each of which has a different type specific polysaccharide antigen in its capsule. These types have been designated types a, b, c, d, e and f respectively. It is of interest that certain types of pneumocci contain capsular polysaccharide antigens which are immunologically related

Diagnosis.—The symptoms and signs which should suggest the diagnosis of meningitis are similar to those described in the section on meningococcic meningitis, except that a purpuric or petechial eruption is practically never seen in H influenzæ meningitis. The spinal fluid is similar to that found in Meningococcus Meningitis except for the difference in bacteriologic findings

Specific etiologic diagnosis of H influenzæ meningitis can be made only by identification of the organism in the spinal fluid In untreated cases these bacteria are almost always demonstrable in Gram-stained smears of the sediment obtained by centrifuging the spinal fluid The presence of small, Gram-negative coccobacilli, together with definite bacillary forms of the organism strongly suggests the proper diagnosis In the great majority of cases, definite identification of H influenzæ can be made by carrying out a Quellung reaction with the spinal fluid sediment, using type a and type b H influenzæ antisera The technique employed for this test is the same as that for Quellung meningococci, except that different antisera are used In 90 per cent of cases, in our experience, capsular swelling occurs with the type b serum A very small percentage of cases of meningitis are caused by type a H influenzæ, and the remaining types are only very rarely the cause of meningitis Confirmation of the result of the Quellung test is made by isolation and identification of the organism from cultures of the spinal fluid and blood, but identification by direct examination of the spinal fluid is by far the most important procedure, since it enables immediate institution of effective specific therapy

Complications and Sequelæ —With the exception of the Waterhouse-Friderichsen syndrome, all the complications described in the section on Meningococcic Meningitis (page 402) are encountered in H influenzæ meningitis In fact, some of these may be more common in H influenzæ meningitis Thus, subdural collections of fluid have occurred more frequently, in our experience, in H influenzæ meningitis than in the meningococcic type

coccus is the causative organism. The symptoms and signs of meningeal irritation, when they are present in H influenzæ infection, are similar to those described in the discussion on meningococcic meningitis Vomiting, irritability, bulging of the fontanelle, stiffness of the neck, convulsions and coma are present Unlike meningococcic meningitis, however, petechiæ and a purpuric eruption are practically never seen, and the Waterhouse-Friderichsen syndrome is very rarely encountered

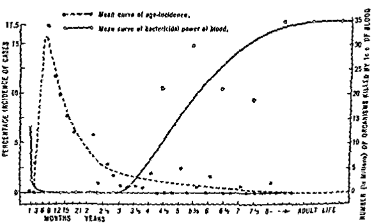


Fig 58 —Relation of age incidence of H influenzæ meningitis to the bactericidal power of human blood at different ages (From Fothergill and Wright, courtesy J Immunology)

In many cases, however, definite signs pointing to involvement of the meninges are lacking. This is especially true in young infants and in those who have received some treatment with antibiotics or sulfonamides H influenzæ meningitis should be kept in mind whenever one is unable to find the cause for fever, and other constitutional signs of infection in a young infant. Under such circumstances a lumbar puncture may be justified in the absence of clinical evidence of meningitis.

tive, and some physicians prefer to use them rather than chloromycetin in combination with sulfadiazine Streptomycin, the first antibiotic found to be of value in the treatment of H. influenzæ meningitis is much less frequently used at present than the other antibiotics mentioned Streptomycin treatment is more likely to be followed by the emergence of antibiotic resistant H influenzæ organisms than is the case with chloramphenicol and the tetracyclines In addition, the risk of injury to the eighth cranial nerve, which sometimes occurs with streptomycin, is not present when the other antibiotics are used Penicillin is effective against some strains of type b H influenzæ *in vitro*, and has been shown to exert a beneficial effect in experimental H influenzæ infection in animals For this reason, a few clinics use penicillin in addition to chloramphenicol and sulfadiazine in the treatment of H. influenzæ meningitis, but it is not recommended that penicillin be used instead of chloramphenicol

Attempts were made by several investigators in the early 1930's to produce an effective therapeutic antiserum against H influenzæ The horse sera produced at this time was found to be ineffective in the treatment of meningitis, probably because the bacteria used to immunize the horses were not fully encapsulated By using organisms which were in a state of optimal encapsulation, Alexander, in 1939, produced a rabbit H influenzæ antiserum which proved to be very effective in meningitis The protective component of this serum is the anticarbohydrate antibody Purified rabbit serum produced commercially according to Alexander's specifications was widely used from 1940 to 1946 When used with sulfadiazine, this type of antiserum reduced the case fatality rate of H influenzæ meningitis to 20 to 30 per cent in contrast with a fatality rate of over 95 per cent among untreated cases The introduction of streptomycin, and later chloramphenicol, made serum therapy much less necessary, and in most clinics, it is not used today However, a number of pediatricians believe that serum therapy should

Prognosis.—The case fatality rate of H. influenzæ meningitis is over 95 per cent among untreated patients, but with modern antibacterial therapy the fatality rate is presently about 5 per cent. However, from 10 to 15 per cent of patients who survive suffer permanent injury to the central nervous system which is detectable on physical examination. The residual injuries include deafness, blindness, severe mental retardation, hemiplegia, hydrocephalus, and convulsive disorders. In addition, it may be that an appreciable number of survivors may suffer a small loss of mental capacity which cannot be documented. In general, the outcome as regards survival and complete recovery is least hopeful among those under six months of age, and it is best among those over three years of age. The prognosis is *clearly better for those treated on the first day of onset of* meningitis than it is for those in whom effective antibacterial therapy has been delayed for a number of days. It is for this reason that prompt, specific diagnosis is so important.

Prophylaxis.—Infants and children under three years old who have been exposed to individuals infected with H. influenzæ should be given chloramphenicol by mouth in dosage of 25 to 50 mgm. per kilogram of body weight per day for five days. Children over three years old should be kept under careful observation for one week after exposure, if they exhibit signs of a respiratory infection during this period, they should receive 100 mgm. of chloramphenicol per day for one week.

There is no method available for active immunization of infants against H. influenzæ.

Isolation and Quarantine.—Patients with H. influenzæ infection should be kept away from infants until the latter have received 48 hours of chloramphenicol treatment. Contacts need not be quarantined.

Treatment.—Chloramphenicol (chloromycetin) combined with sulfadiazine are the antibacterial drugs used by most physicians with a large experience in the treatment of this disease. However, the tetracycline drugs are also very effec-

in 0.85 per cent saline solution during the next 24 hours. One hundred mgm. per kilogram of body weight are given at 12-hour intervals for two doses to infants and very small children and one-half this dosage to older children and adults. After this, sulfadiazine is given by mouth, in dosage sufficient to produce a blood concentration of 10 to 15 mgm. per cent. Two hundred to 300 mgm. per kilogram per day are given to infants and 100 to 150 mgm. per kilogram per day to older children, and 100 mgm. per kilogram per day for adults (not exceeding a total of 6 grams). Care must be taken to supply an adequate fluid intake in order to lessen the risk of sulfadiazine injury to the kidneys, as well as for the other reasons already discussed in the section on Meningococcic Meningitis (page 419).

Forty-eight hours after beginning therapy, a specimen of spinal fluid is obtained by lumbar puncture. Its cell content and sugar concentration are determined, and an examination is made by smear and culture for the presence of organisms. When the response to therapy is satisfactory, this spinal fluid specimen is sterile, its sugar concentration is definitely higher than the initial value, the number of cells is smaller, and the predominance of polymorphonuclear cells is greatly reduced or absent.

Another spinal fluid specimen is obtained on the seventh day after beginning treatment. When the patient's progress has been satisfactory, this spinal fluid has a normal sugar concentration, and smears and cultures show an absence of bacteria. The number of cells may vary from zero to 200 but they are practically all mononuclear.

Chloramphenicol and sulfadiazine may be discontinued at the end of seven days of treatment if the patient's clinical condition indicates that he is well on the way to recovery, provided that examinations of the spinal fluid obtained on the second and seventh day support this clinical impression.

When it is decided to use type specific rabbit serum in addition to chloramphenicol and sulfadiazine (see page 429), the following regimen is recommended: Test for sensitivity

be re-evaluated in order to determine whether or not its inclusion in the treatment regimen might be of value for infants under six months of age and extremely ill patients who are over six months old.

Early recognition of the clinical signs of meningitis and very prompt identification of H. influenzæ in the spinal fluid are essential since the best results can be obtained only by early and adequate treatment. As soon as it is seen that the spinal fluid is cloudy, a 5 per cent solution of sodium sulfadiazine is given intravenously in a dosage of 40 mgm per kilogram of body weight When H influenzæ organisms are identified (by direct examination of the spinal fluid), chloramphenicol is given immediately by intravenous injection, in a dose of 50 mgm per kilogram, and in addition, the same dose is given intramuscularly. *Chloramphenicol used for intravenous injection is prepared and administered in the following manner:*

0 5 grams of chloramphenicol in 2 ml. of a special diluent (N,N-dimethyl acetamide solution) is drawn up into a syringe The needle used in this procedure is replaced by a new one The chloramphenicol is then rapidly introduced into 100 ml. of a sterile solution of NaCl (0 85 per cent), the needle being held below the surface of the saline to avoid formation of a harmful precipitate The proper dose of chloramphenicol is then given by slow intravenous drip

After the initial intravenous and intramuscular injections, chloramphenicol therapy is continued by intramuscular injection for the next two days, 50 mgm. per kilogram being given twice daily. At the end of this course of treatment (a total of one intravenous and 5 intramuscular injections) chloramphenicol is administered by mouth in dosage of 150 to 200 mgm. per kilogram per day, divided into 4 doses Any chloramphenicol preparation available for oral use may be employed, except chloromycetin palmitate, which is sometimes poorly absorbed from the intestine.

After the initial intravenous administration, sodium sulfadiazine is given subcutaneously in a 1 per cent concentration

described in the section on H influenzæ meningitis A few petechiæ may be seen on the skin, but a purpuric rash such as occurs in meningococcic infections is very unusual The specific etiologic diagnosis of pneumococcic or streptococcic meningitis can only be made by bacteriologic examination Practically always, the organisms can be found in smears of the spinal fluid of untreated patients They appear as Gram-positive cocci in pairs or in chains Pneumococci can be identified with certainty by the Quellung reaction with type specific antisera. Cultures of spinal fluid from these cases nearly always yield the pneumococci or streptococci in profusion, thus confirming the diagnosis made on direct examination of smears of the spinal fluid

Complications and Sequelæ.—These are similar to those encountered in H influenzæ meningitis.

Prognosis.—As in the case of H. influenzæ meningitis, the prognosis depends largely upon the age of the patient and the duration of the disease before proper treatment is started In general, in our experience, the prognosis is worse in pneumococcic and streptococcic meningitis than it is when H influenzæ is the causative organism. In addition, we have the impression that the incidence of serious sequelæ is greater in pneumococcic and streptococcic types of meningitis.

Treatment—Early diagnosis and prompt institution of antibacterial therapy is essential Most clinics employ very large doses of penicillin together with sulfadiazine in the treatment of pneumococcic and streptococcic meningitis Some authors recommend the use of chloramphenicol in addition Sulfadiazine should be given in a quantity sufficient to produce a blood concentration of 10 to 15 mgm per cent This drug is administered in the same manner as that described under the treatment of H influenzæ meningitis Aqueous crystalline penicillin is given by continuous intravenous drip for the first three days of therapy, 4 to 12 million units are given daily Only aqueous crystalline penicillin is suitable for intravenous injection After three days of this penicillin therapy have been completed, aqueous pro-

to rabbit serum, using the ophthalmic test with a 1 to 10 dilution of the serum. If this is negative, give the serum by intramuscular injection, intravenous and intrathecal injections are not recommended. The dose of serum varies from 50 to 100 mgm. of antibody nitrogen, given in a single injection. Eight hours after the injection, the patient's serum should be tested for the presence of free anticarbohydrate antibody. This is done by mixing a drop of his serum (diluted 1 to 2 with 0.85 per cent NaCl solution) with a small number of *H. influenzæ* organisms obtained by centrifugation of a six- to eight-hour culture. Capsular swelling (Quellung) of the organism indicates that the patient's blood contains a sufficient quantity of antibody, and that the dose of rabbit serum given is adequate. If no Quellung reaction is demonstrated, a second dose of serum, half as large as the first, should be administered, unless there is clinical evidence of marked improvement.

Treatment of the complications of *H. influenzæ* meningitis is the same as that of the complications which occur in meningococcic meningitis.

PNEUMOCOCCIC AND STREPTOCOCCIC MENINGITIS

These types of meningitis may follow septicemia and bacterial embolization of the blood vessels of the meninges. In addition, pneumococcic and streptococcic meningitis may result from spread of infection from the middle ear, mastoid cells and sinuses to the meninges. Pneumococci of every type may cause meningitis, group A Beta-hemolytic streptococci account for the vast majority of cases of streptococcic meningitis.

The clinical course of meningitis due either to pneumococcic or streptococcic infection is very similar to that due to *H. influenzæ* but in each case the incidence is less sharply limited to infants and young children.

Diagnosis.—The clinical symptoms and physical signs which suggest the diagnosis of meningitis are similar to those

described in the section on H. influenzæ meningitis. A few petechiæ may be seen on the skin, but a purpuric rash such as occurs in meningococcic infections is very unusual. The specific etiologic diagnosis of pneumococcic or streptococcic meningitis can only be made by bacteriologic examination. Practically always, the organisms can be found in smears of the spinal fluid of untreated patients. They appear as Gram-positive cocci in pairs or in chains. Pneumococci can be identified with certainty by the Quellung reaction with type specific antisera. Cultures of spinal fluid from these cases nearly always yield the pneumococci or streptococci in profusion, thus confirming the diagnosis made on direct examination of smears of the spinal fluid.

Complications and Sequelæ.—These are similar to those encountered in H. influenzæ meningitis.

Prognosis.—As in the case of H. influenzæ meningitis, the prognosis depends largely upon the age of the patient and the duration of the disease before proper treatment is started. In general, in our experience, the prognosis is worse in pneumococcic and streptococcic meningitis than it is when H. influenzæ is the causative organism. In addition, we have the impression that the incidence of serious sequelæ is greater in pneumococcic and streptococcic types of meningitis.

Treatment.—Early diagnosis and prompt institution of antibacterial therapy is essential. Most clinics employ very large doses of penicillin together with sulfadiazine in the treatment of pneumococcic and streptococcic meningitis. Some authors recommend the use of chloramphenicol in addition. Sulfadiazine should be given in a quantity sufficient to produce a blood concentration of 10 to 15 mgm. per cent. This drug is administered in the same manner as that described under the treatment of H. influenzæ meningitis. Aqueous crystalline penicillin is given by continuous intravenous drip for the first three days of therapy; 4 to 12

caine penicillin is given intramuscularly in a dosage of 1 million units twice daily. We do not recommend intrathecal injection of penicillin since this method of administration is attended by some risk of injury to the central nervous system, and it appears that results are not improved by this procedure.

All therapy may be discontinued after seven days of treatment have been completed provided the patient's clinical course is satisfactory, and provided that a spinal fluid specimen obtained two days after the beginning of therapy is sterile, and also that the spinal fluid obtained on the seventh day of treatment is sterile and contains a normal sugar concentration

BACTERIAL MENINGITIS OF UNDETERMINED ORIGIN

At the present time a large percentage of meningitis patients admitted to the hospital have previously been treated with one or more antibiotics Very often patients are given antibiotics in the early stages of meningitis without realization on the part of the physician that this condition exists The patient may therefore be treated for an upper respiratory infection and consequently may be given only a relatively small dose of antibiotic In other instances, the antibiotic used may be one which is not entirely effective against the organism causing the meningitis In such cases, there may be temporary improvement, but when the antibiotic is withdrawn, evidences of a severe infection and signs of meningitis may appear Under these circumstances, the causative organisms may be so few in number that they cannot be found on microscopic examination of smears of the spinal fluid. In addition, because of the presence of antibiotic in the spinal fluid, they may fail to grow out in cultures.

When the physician cannot find the causative organism in the direct examination of the spinal fluid, he must institute treatment on the supposition that the causative organism is actually H influenzae, pneumococcic or streptococcic menin-

gitis. This means that he must employ sulfadiazine and chloramphenicol (as if H. influenzæ organisms were present), and very large doses of aqueous crystalline penicillin given intravenously (as if pneumococcic or streptococcic organisms were present). Treatment with these three drugs should be continued for a period of at least seven days.

MENINGITIS DURING THE FIRST MONTH OF LIFE

During the neonatal period, organisms of the family Enterobacteriaceæ are the most common cause of meningitis, as contrasted with the situation in older infants, in which H influenzæ causes most cases of meningitis. In our experience, E coli (colon bacillus) is responsible for most of the cases of neonatal meningitis Various strains of E coli differ greatly in their sensitivity to available antibiotics so that it is very difficult to decide which drug should be used to begin treatment in a given case. Our policy is to begin therapy with sulfadiazine and chloramphenicol as described in the treatment of H influenzæ meningitis, and to determine as quickly as possible (by *in vitro* tests) which antibiotic is most likely to be clinically effective In a number of instances, change from chloramphenicol to neomycin has been followed by prompt improvement. The dose of neomycin is 2 5 mg. per kilogram of body weight given four times daily by intramuscular injection.

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15

Poliomyelitis

From the Greek words πολιός (polios) meaning "gray;" μυελός (myelos) meaning "marrow" and hence spinal cord; with the suffix "itis" meaning inflammation; hence inflammation of the gray matter of the spinal cord

Synonyms.—Acute anterior poliomyelitis; infantile paralysis, Heine-Medin disease.

Definition.—An acute infection, caused by three related, but immunologically distinct viruses In the vast majority of cases (about 90 per cent), infection with these viruses causes no apparent illness, and is followed by immunity. Five to 8 per cent of those infected become ill with fever and respiratory or gastrointestinal symptoms, but with no *neurologic manifestations Finally, in about 2 per cent of* persons infected with poliomyelitis virus, signs of invasion of the central nervous system follow the respiratory and gastrointestinal symptoms which may have been minimal. In these cases, the virus enters the central nervous system and becomes distributed through it The outstanding clinical features of involvement of the central nervous system are weakness and flaccid paralysis of the striated muscles caused by injury of the anterior horn cells of the spinal cord and the nuclei of the cranial nerves.

THE ETIOLOGY OF POLIOMYELITIS

In 1909 Landsteiner and Popper succeeded in transmitting the disease from man to monkey by the intraperitoneal injection of a bacteria-free filtrate of an emulsion of the spinal

cord of a child who had died of poliomyelitis. Intracerebral inoculation was later used successfully by Flexner, who also transmitted the disease from monkey to monkey. Thus a method was obtained by which the infection could be constantly produced, and an opportunity was furnished for studying various aspects of the causative virus, its nature, methods of entrance and exit, distribution through the body, and powers of immunization.

Then, in 1949, Enders and co-workers propagated poliomyelitis viruses in tissue cultures of human embryo skin and muscle, and intestine, as well as nerve tissue. Later it was shown that polioviruses can be grown in cultures of a variety of human tissues such as the prepuce of young infants, and cancer cells (HeLa cells) and in monkey testicular and monkey kidney tissue. Growth of the virus is accompanied by injury and death of the cells (cytopathogenic effect). Serum containing type-specific antibody prevents the growth of the virus in tissue culture and prevents the cytopathogenic action of the virus (virus neutralization). Hence, the tissue culture method is now of great value as a diagnostic tool. By its use, the presence of poliovirus can be detected in feces, and the development of antibodies in the blood during convalescence can be shown. In addition, large quantities of polioviruses grown in tissue culture have been used in the preparation of a vaccine.

Types of Poliomyelitis Virus.—Three types of poliomyelitis viruses are currently known. These are named type 1 (Brunhilde), type 2 (Lansing), and type 3 (Leon), poliovirus respectively. All types produce identical pathologic changes in the central nervous system of man and monkeys, and the clinical disease caused by a given type cannot be distinguished from that caused by the other types. Despite this, the three polioviruses do not produce solid cross immunity in monkeys, and the same is true in man. Thus, an animal which has

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utes for disinfection of drinking water. Other authorities believe that 1.0 to 1.5 parts of chlorine per million are required to inactivate polioviruses (a concentration greater than ordinarily used to purify water).

Polioviruses remain viable in glycerine at 4° C. and in the frozen state for very long periods. Their activity has been shown to persist for long periods in feces, in water and in milk kept at refrigerator temperatures They are readily destroyed by drying when contained in small droplets in air of low humidity at usual room temperatures All types of polioviruses are pathogenic for man but no other species is attacked in nature In the laboratory, however, all types of polioviruses cause disease in certain species of monkeys (Macaca rhesus and Macaca cynomolgus), and in chimpanzees. Experimental infection of rodents (cotton rats, mice and hamsters) can be produced by type 2 virus

THE PATHOGENESIS OF POLIOMYELITIS

It was formerly considered that the nasal mucosa was the portal of entry for the polioviruses, but a great deal of evidence is now available that this is not the case It is now believed that they gain access to the body by the oral cavity and the alimentary tract The evidence pointing to the alimentary tract (which includes mouth, and pharynx, as well as stomach and intestines), seems quite convincing It includes the fact that poliovirus is present in the oral secretions during the first week of the disease, and in the feces during the acute illness—as well as during *convalescence* (see Fig 59) Experimental as well as clinical observations support the idea that the alimentary tract is the site of entry For example, Macaca cynomolgus monkeys and chimpanzees can be infected by feeding poliovirus Poliomyelitis can also be produced in animals by subcutaneous injection of the virus, and accidental infection in man following subcutaneous and intramuscular injection of vaccines containing active virus is well documented It is probable, however, that infection through the skin is not the usual means of infection.

who have suffered paralytic poliomyelitis from more than one type of poliovirus. However, there is some reason to believe that the immunologic response to poliovirus infection is not entirely type specific in human beings. A number of children infected with type 1 poliovirus have developed low titers of antibody against types 2 and 3 also There is some evidence that type 2 poliovirus is usually endemically present, while types 1 and 3 show a more cyclic pattern, being more often associated with epidemics

Properties of Poliomyelitis Viruses.—The polioviruses are small viruses, their size having been estimated from filtration experiments to be 8 to 12 mu However, this value is based partly on empiric calculations which are not entirely accurate, and data obtained by centrifugation experiments show that the polioviruses may be approximately 30 mu. in size Electron microscope pictures show the dried virus particles to be roughly spherical in shape.

The exact chemical nature of the polioviruses has not been determined since no analyses of sufficiently pure preparations have been carried out. It is probable that polioviruses, like other viruses, are essentially proteins, and one strain of poliovirus has been found to have the ultraviolet absorption properties of nucleoproteins. Recently type 1 poliovirus has been purified and crystallized without loss of its infectious properties.

Polioviruses are resistant to certain chemicals, such as ether, and low concentrations of phenol. The virus is destroyed by heating at 55° C. for thirty minutes, and at 60° C for seven minutes. Polioviruses are rendered non-infectious by exposure to ultraviolet light and by treatment with formaldehyde. They are destroyed by such oxidizing agents as hydrogen peroxide and potassium permanganate Chlorine destroys polioviruses, the concentration required depending in part upon the amount of organic matter present in suspension with the virus. The United States Public Health Service recommends a residual chlorine concentration of 0.2 part per million maintained for at least twenty min-

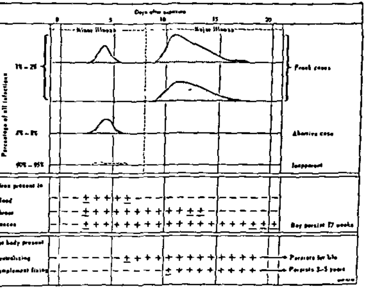
utes for disinfection of drinking water. Other authorities believe that 1.0 to 1.5 parts of chlorine per million are required to inactivate polioviruses (a concentration greater than ordinarily used to purify water).

Polioviruses remain viable in glycerine at 4° C. and in the frozen state for very long periods. Their activity has been shown to persist for long periods in feces, in water and in milk kept at refrigerator temperatures. They are readily destroyed by drying when contained in small droplets in air of low humidity at usual room temperatures. All types of polioviruses are pathogenic for man but no other species is attacked in nature. In the laboratory, however, all types of polioviruses cause disease in certain species of monkeys (Macaca rhesus and Macaca cynomolgus), and in chimpanzees. Experimental infection of rodents (cotton rats, mice and hamsters) can be produced by type 2 virus.

THE PATHOGENESIS OF POLIOMYELITIS

It was formerly considered that the nasal mucosa was the portal of entry for the polioviruses, but a great deal of evidence is now available that this is not the case. It is now believed that they gain access to the body by the oral cavity and the alimentary tract. The evidence pointing to the alimentary tract (which includes mouth, and pharynx, as well as stomach and intestines), seems quite convincing. It includes the fact that poliovirus is present in the oral secretions during the first week of the disease, and in the feces during the acute illness—as well as during *convalescence* (see Fig. 59). Experimental as well as clinical observations support the idea that the alimentary tract is the site of entry. For example, Macaca cynomolgus monkeys and chimpanzees can be infected by feeding poliovirus. Poliomyelitis can also be produced in animals by subcutaneous injection of the virus, and accidental infection in man following subcutaneous and

The entry of the virus into the alimentary canal causes no illness to persons who are immune as the result of previous contact with the virus. The same is true of young infants who still possess passive immunity due to maternal antibody. In addition, no illness results in the vast majority of individuals even without evidence of previous infection with poliovirus. The virus may establish itself in the alimentary



Shaded areas denote periods of fever

FIG. 59.—Schematic diagrams of the clinical and subclinical forms of poliomyelitis, showing presence of virus and antibodies in relation to the development and subsidence of the infection. (*Poliomyelitis*, Debré *et al* courtesy of the World Health Organization.)

tract, and be excreted in the stools without causing noticeable illness. In about 10 per cent of those coming into contact with poliovirus, a recognizable illness does result, but signs of central nervous system disease occur in only approximately one-fifth of these latter persons.

The virus probably invades the blood stream in all cases in which symptoms of central nervous system disease occurs

In addition, a recent survey has shown that poliovirus is present in the blood of patients who suffer only an "abortive attack" (minor illness) of poliomyelitis. In this study, an investigation was made of the blood of nine children who were household contacts of type 1 poliomyelitis patients. None of the nine children had antibody against type 1 poliovirus, and this virus was isolated from the blood of five of them. Four of these five children suffered a minor illness, but did not exhibit any signs of involvement of the nervous system

The viremia of poliomyelitis is present late in the incubation period and in the first few days after the onset of clinical manifestations It is not known whether poliovirus invades the blood directly from the alimentary tract or whether the viremia is merely a spill-over from other tissues in which the virus is present, such as the pharynx, the large and small intestine, mesenteric lymph glands, and "brown fat" (a special type of fat found in the axilla and pretracheal fascia). The *hypothesis of the pathogenesis of poliomyelitis put forward* by Bodian and by Horstmann assumes that poliomyelitis is primarily an intestinal infection In the immune person, antibody in the blood prevents the invasion of the blood (or overcomes it), but it does not prevent the intestinal infection. In the non-immune, no protective antibody is present, so that intestinal infection is followed by viremia

Viremia is postulated as the method by which invasion of the central nervous system occurs. The theory of the sequence of intestinal infection viremia, and central nervous system invasion fits many of the known facts of natural and experimental poliomyelitis However, some clinical and experimental data do not seem to conform exactly to the theory For example, viremia is not always followed by invasion of the central nervous system and one must suppose that in such cases some mechanism other than neutralization of virus protects the central nervous system from injury. A "blood-brain" barrier may be an explanation of this phenomenon. Furthermore, it is known that certain nonspecific factors such as fatigue, trauma, and (in animals) adrenal

steroids may determine whether or not the central nervous system becomes involved and perhaps even what may be the location and extent of neurone injury

Polioviruses leave the human body both by way of the stools and by way of material expelled from the mouth. It is known that the excretion of virus in the stools persists for a longer period than in the secretions of mouth and throat Thus it is seldom possible to isolate virus from the latter site after the first week of illness, whereas from the sixth to eighth week, virus has been detected in the stools of 12 per cent of patients, and it has been found once in the stool of a patient as late as the seventeenth week Virus has been isolated, furthermore, from the stool of an individual nineteen days before the onset of disease. Poliovirus has never been found in the spinal fluid or in the urine.

THE HISTORY AND EPIDEMIOLOGY OF POLIOMYELITIS

Poliomyelitis probably occurred in ancient Egypt, at least as early as 1300 B C , and Hippocrates mentions paralysis of the legs attacking many in the summer and early autumn It is clear, however, that in ancient times poliomyelitis was not an important epidemic disease Acute paralysis in infants, as a disease entity, began to be described late in the 18th, and in the early part of the 19th century By 1825, it had been recognized in England, Italy, and India The cause of the disease was not known, and no idea was expressed that it might be contagious In 1840, Heine studied a number of late paralytic cases, and he wrote the first systematic description of the disease. Until the middle of the nineteenth century, poliomyelitis was almost entirely limited to infants and it was an endemic and not an epidemic disease. However, epidemics began to appear with increasing frequency after 1865. In 1868, a group of 14 cases was reported from Norway. In 1887, Medin described an epidemic of 44 cases in Stockholm, and in 1888 Cordier reported an outbreak in

France. Caverly recorded the Vermont epidemic of 1894 In 1905, Wickman outlined the epidemiologic concept of the disease which, in its essentials, is held today He pointed out the infectious nature of the disease, and showed that it was spread by human contact. Of great importance was his conclusion that poliomyelitis may be spread by healthy carriers, and by patients with a mild attack of the disease, as well as by those with the severe paralytic form

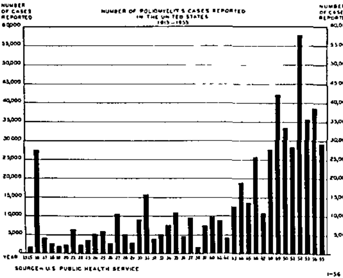


FIG 60 —Infantile paralysis cases reported in the United States—1915–1955 (Courtesy of the National Foundation for Infantile Paralysis)

Since 1900, epidemics have occurred with increasing frequency in Europe, North America and other temperate zones, and this pattern has persisted in these areas to the present time Thus, in the United States, there was a gradual development from sporadic cases to an epidemic form of the disease in 1905, with frequent epidemics since then During the past thirty years or so, more than half of the known cases

of the world have been reported from the United States and adjacent parts of Canada. New York City and vicinity was visited in 1916 by the largest local epidemic yet recorded, practically 9000 cases occurring during the summer. The death-rate was 26.9 per cent. Many other communities were also afflicted at this time, there having been 27,363 cases in the United States that year. A number of other but lesser epidemics have occurred since, notably in 1931, 1946, and each year since 1948, with 1952 the heaviest year on record in the United States, although all with much lower death-rates, probably largely because of the recent inclusion in the statistics of many non-paralytic cases, a type formerly not diagnosed.

Congested districts are apparently immunized readily by the ever-present virus, and after a severe epidemic a city is usually comparatively free for several years. City dwellers are likely to be exposed to the disease earlier in life than are country people. Hence the more isolated the community the higher the incidence of the disease in an epidemic, and the older the average age of the patient. Friedemann mentioned a remarkable outbreak of poliomyelitis on a Pacific Island during which 37 per cent of the natives were affected, and the greatest incidence was between the ages of twelve and forty years. In 1948 and 1949, an epidemic of poliomyelitis occurred among the Eskimos in the Canadian Arctic. In the remote town of Chesterfield Inlet, on Hudson's Bay, 60 per cent of the entire population suffered an attack of poliomyelitis, with all age groups being involved. However, even in severe epidemics in more heavily populated areas, the ratio of recognized cases of the disease to the total population is practically always small, in large communities rarely being more than 1 case per 1000 population. In 1916, 1.59 per 1000 had the disease in New York City, and 2.4 in the rural districts. Twenty-two to 29 per cent of all crippling due to neuromuscular diseases is said to be due to poliomyelitis.

Transmission and Spread.—Within the past twenty years, the epidemic pattern of poliomyelitis has appeared in some

semi-tropical regions such as Puerto Rico, Hawaii, and Malta. However, in most tropical and subtropical parts of the world, epidemics of poliomyelitis are unusual and the disease is endemic in character. This is particularly the case in tropical cities with poor sanitary facilities In these regions, the disease is still almost entirely limited to infants and children five years of age or less In such communities, crowding is great and sanitation is poor Consequently, exposure during the early years of life to fecal matter which contains poliomyelitis virus is much greater than is the case in the cities of North America, Western Europe and Australia For example, in Cairo, an extremely crowded city with very poor sanitary conditions, practically all children have acquired antibodies against poliomyelitis viruses by the time they are five or six years old By this age, they have reached maturity as far as immunity to poliomyelitis goes, and virtually all the paralytic cases of the disease which are going to occur in this population have already been experienced As a result there is no threat of the disease in adolescence or adult life

As just stated, this early immunologic maturity is reached by heavy and repeated exposure during the early years of life Furthermore, much of the exposure takes place in the first months after birth, when antibody from the mother may act as a passive protective mechanism, and the poliomyelitis infection is very largely clinically inapparent In contrast is the experience of children in cities with better sanitary facilities, and less crowded conditions. The immunologic maturation against poliomyelitis of the child population in American cities is much delayed This is shown in the accompanying chart, which compares the experience of Cairo with that of Miami, which is in the same latitude[1] In Cairo antibody against poliomyelitis virus is present in the serum of nearly 100 per cent of children over 4 years old, and practically all clinical cases of poliomyelitis have oc-

[1] From J R Paul, Chapter on Epidemiology of Poliomyelitis, in Poliomyelitis, World Health Organization Monograph, Geneva, 1955 (page 24)

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as well as the frank case (paralytic, or non-paralytic) Paralytic patients may be especially dangerous, however, since they excrete very large quantities of poliovirus in the stools. On the other hand, healthy carriers and abortive cases are epidemiologically more important because they are so much more numerous than paralytic patients and are not recognized.

The virus spreads with great rapidity among the population of a contaminated district but the morbidity is low, most people being immunized without developing clinical manifestations. It has been estimated that the ratio of frank cases (paralytic and non-paralytic) to "abortive cases" is about 1 to 7 Data from several sources suggest that the ratio of paralytic cases (excluding non-paralytic) to clinically inapparent infections is about 1 to 100. Cases with a clear history of causative contact are unusual Radial spread is definite and best explained by passage from person to person The incidence wanes in the central focus while increasing in the outer concentric zones, with an exhaustion of susceptibles in the central area

It is certain that direct person to person contact accounts for much of the spread of poliomyelitis However, this cannot explain all of the known facts regarding the epidemiology of poliomyelitis One of these mysteries is the high incidence of the disease in the summer and early fall There are several possible explanations of this phenomenon These include the possibility that the weather of summer may favor the introduction of the virus into a community, while winter weather may be unfavorable to such an occurrence Warm weather may increase the ease with which virus spreads from person to person, or it may decrease the resistance of non-immune individuals to infection, while the cold weather of winter may have the opposite effect Facts to support these hypotheses are lacking

As Paul has stated, man not only contaminates his fellow associates, but also his immediate environment with poliomyelitis virus An example of this is the presence of polio-

curred by the time this age has been reached. In Miami the production of antibody is much slower, only 80 per cent of persons being positive at 20 years of age, and not all clinical cases have been experienced until the population age has reached 35 years

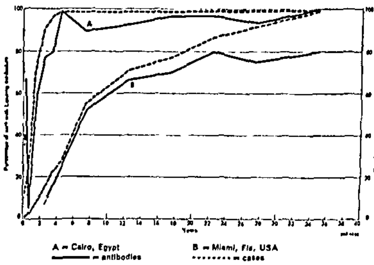


FIG 61 —Comparison of type-2 neutralizing antibody pattern with cumulative attack-rate of poliomyelitis in populations from two subtropical areas (*Poliomyelitis*, Debré *et al*, courtesy of the World Health Organization)

The exact manner in which poliomyelitis virus is transferred from an infected person to another is not known During the first week of illness, virus is excreted both from the pharynx and from the intestines but after this period only intestinal (fecal) excretion occurs, and this may continue for weeks and months. However, long-term carriers, who excrete virus for years, have not been found. Persons with any form of poliomyelitis infection excrete virus, and may be responsible for the spread of infection. This is true of the healthy carrier, and of the person with a minor illness not clinically recognizable as poliomyelitis ("abortive case"),

as well as the frank case (paralytic, or non-paralytic) Paralytic patients may be especially dangerous, however, since they excrete very large quantities of poliovirus in the stools On the other hand, healthy carriers and abortive cases are epidemiologically more important because they are so much more numerous than paralytic patients and are not recognized

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contaminates his fellow associates, but also his *immediate environment* with poliomyelitis virus An example of this is the presence of polio-

virus in urban sewage and in fecal material from privies This does not mean that sewage is the usual means by which poliomyelitis infection is spread through a community, but it does show evidence of poliovirus infection in the community The possibility that contamination of the water supply might cause widespread poliomyelitis infection has been discussed by Kling, but there is little evidence that such an occurrence has actually taken place. In only a few outbreaks has there been reason to consider that contaminated milk has been responsible for dissemination of poliomyelitis

Insects and other arthropods have been suspected of being involved in the spread of poliomyelitis, and poliovirus has been found in flies and cockroaches A number of species of flies have been found to harbor the virus, this being true particularly of those which feed on fecal matter. Although the virus does not multiply in these insects, it is possible that they may act as mechanical agents to contaminate food with a quantity of virus sufficient to cause infection There is no reason, however, to believe that flies play the main role in the spread of poliomyelitis, and some epidemics (in the Arctic) have occurred despite the complete absence of flies The finding that viremia is common in the early stages of poliomyelitis has caused renewed interest in mosquitoes as possible vectors of poliomyelitis, but no evidence has yet been found which points to these insects as being involved in the spread of poliomyelitis

Family Incidence —Formerly there was usually but one recognized case of poliomyelitis in a household. In certain epidemics, however, multiple paralytic cases in an appreciable number of families were reported, and in the 1916 epidemic, 4 per cent of the afflicted families had more than one case In more recent years it has become recognized that poliomyelitis infection of the entire family is common, although only one member may show clinical symptoms recognizable as poliomyelitis. *However, multiple clinical cases are not rare, and* one instance is recorded in which 9 children in one family suffered recognizable attacks of clinical poliomyelitis Most

family cases are concurrent, that is, apparently due to the same exposure, rather than consecutive, one causing the other.

Age.—The incidence of poliomyelitis varies with age, this variation being a reflection of the percentage of the various age groups who possess antibody against the polioviruses. The change of poliomyelitis *from an endemic to an epidemic* disease has been accompanied by a gradual change in the age incidence. In the endemic phase of the evolution of polio-

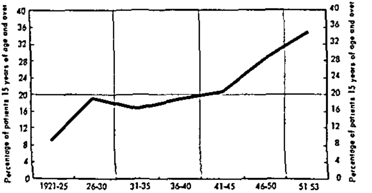


FIG. 62.—The rising age of poliomyelitis patients in Connecticut, U.S.A. (*Poliomyelitis*, Debré *et al.*, courtesy of the World Health Organization.)

myelitis, nearly 90 per cent of the paralytic cases in Northern Europe and North America were infants, the maximal attack rate being in the 0 to 4 year age group. At the present time, in temperate zones, the highest attack rate occurs among those 5 to 9 years old, and in some countries (Sweden) among the 7 to 15 year old group. There has also been a steady increase in the relative frequency of the disease in adolescents and adults. In the northeastern part of the United States at the present time, as many as 35 per cent of poliomyelitis patients are over 15 years old. Figure 62 shows this trend. In Connecticut only 9 per cent of polio-

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from 55 to 60 per cent boys There is no particular racial susceptibility.

Season — Poliomyelitis is at its maximum in the later warm months, July and August in the northern hemisphere, the

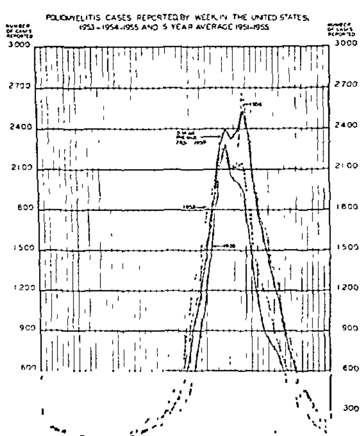


FIG 63 —Weekly incidence of *infantile paralysis in the United States*— 1951-1955 (Courtesy of the National Foundation for Infantile Paralysis)

myelitis patients were 15 years old or more in 1921 to 1925, while 35 per cent in 1951 to 1953 were in that age group The adolescent and young adult therefore must now be considered to be highly susceptible to poliomyelitis. Furthermore, the disease tends to be more serious in these age groups, the fatality rate for young adults being from 2 to 5 times greater than it is for children under 7 years of age. The explanation for this is in part that bulbar involvement and respiratory muscle paralysis occur in a much higher percentage of adult poliomyelitis patients than they do among children with this disease

Newborn infants are immune to poliomyelitis if they are born of immune mothers, who provide them with placentally transmitted polio antibodies. The immunity is a passive one, however, and is not effective beyond the fifth or sixth month of life Since most women of childbearing age do possess antibody against polioviruses, it follows that most infants will be immune for the first six months of life[1] However, babies born of non-immune mothers are susceptible to the disease, and paralytic poliomyelitis occurring during the neonatal period can no longer be considered extremely rare Bates, in his review of this subject in 1955, recorded 56 cases of poliomyelitis occurring in the first three weeks of life We have encountered several cases of paralytic poliomyelitis of the newborn which have not been reported Several undoubted instances of intrauterine poliomyelitic infection have been described In the case of one infant who died when 13 hours old, the diagnosis of poliomyelitis was confirmed by histologic examination of the nervous system On several occasions newborn infants of mothers suffering from poliomyelitis were proven by isolation of poliovirus to be similarly affected.

Sex.—In most epidemics, the proportion of boys attacked is slightly higher than that of girls, the usual figure being

[1] Fox *et al* (1956) state that maternally derived antibody does not persist for more than three months unless the maternal antibody titer was unusually high



FIG. 64 — *Top* Late changes of [illegible]

[illegible]

flammatory cells or edema in the vicinity

Bottom Irreversibly damaged motoneuron, shrunken hyperchromatic cell with vacuolated cytoplasm, pyknotic nucleus and beginning neuronophagia (× 487) (Bodian, *Poliomyelitis Conference*, courtesy of J B Lippincott Co and Intern Poliomyelitis Congress)

epidemics usually running on into September, October and sometimes November The onset of an epidemic is often signalled by a sharp increase of cases some week in May or June The disease also occurs sporadically in winter, and with a higher case fatality-rate than in summer. Thus, poliomyelitis is considered a disease which occurs the year around but with much greater incidence in the harvest season.

THE PATHOLOGY OF POLIOMYELITIS

Central Nervous System.—*At autopsy in patients dying in the early stages of the disease, the brain on gross examination appears swollen, and the cord, when sectioned, bulges out over the cut edges It is not certain, however, that this swelling of the nervous system is due to edema*

When poliovirus invades the central nervous system, it produces lesions which are of a quite specific nature and the distribution of these lesions is characteristic In the spinal cord, the virus causes lesions mainly in the anterior horn cells, but the cells of the autonomic and sensory columns of the cord are also affected, although to a lesser degree In patients who succumb to poliomyelitis, the virus is also found in the brain, and evidence of extensive encephalitis is present The motor cells of the reticular formation of the pons and medulla and the vestibular nuclei in the cerebellum are regularly affected. The virus also injures the cells of the cerebral cortex, but only the motor and premotor areas are involved. No part of the visual system, including the optic nerve, is affected, and the auditory projection areas and the cortical association areas are spared

In experimental animals, virus activity cannot be detected in the central nervous system until microscopic lesions are present. Multiplication of the virus and the pathologic changes precede the beginning of paralysis by one to several days. The virus attack is primarily upon the neurones which suffer injury from the direct action of the virus, and not from the edema and inflammatory reaction The polio viruses do

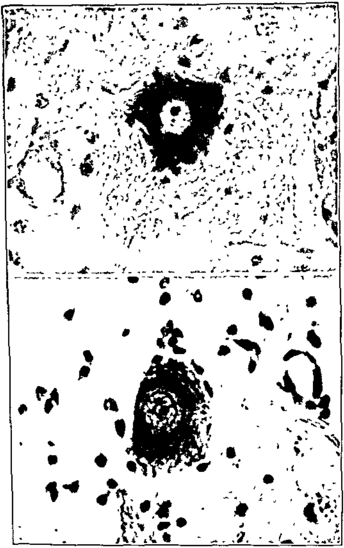


FIG 64 —*Top* Late changes of chromatolysis, probably compatible with recovery (rhesus monkey) Disappearance of Nissl bodies with faint, diffuse cytoplasmic basophilia Shrunken nucleus contains a single large eosinophilic inclusion body and an intact nucleolus Note absence of in-

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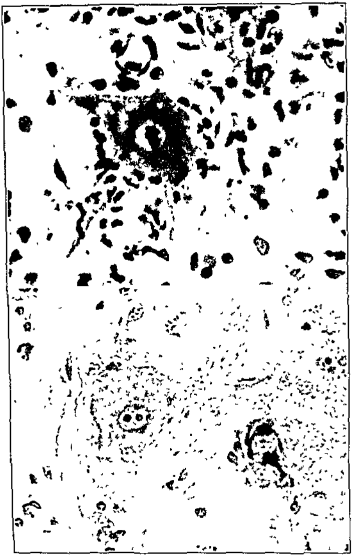


FIG 66 —*Top* Normal anterior horn cell of a rhesus monkey Note massive Nissl bodies in cytoplasm, central position of nucleus, large basophilic nucleolus and dispersed chromatin

Bottom Early stage of motoneuron injury of a rhesus monkey infected with polio virus Note diffuse decrease in size of Nissl bodies (chromatolysis) and essentially normal nucleus (× 487) (Bodian, *Poliomyelitis Conference*, courtesy of J B Lippincott Co and Intern Poliomyelitis Congress)





Fig. 66 — *Top* Normal anterior horn cell of a rhesus monkey Note massive Nissl bodies in cytoplasm, central position of nucleus, large baso-

Conference, courtesy of J B Lippincott Co and Intern Poliomyelitis Congress)



disease, inflammatory changes may be so marked and so widespread that they give a false impression of the basic fundamental pathology A chronologic examination of the pathologic changes which occur in the central nervous system, however, makes it clear that inflammatory changes and edema, although they may be very marked, are only secondary phenomena.

Distribution.—Only in certain susceptible parts of the central nervous system do neuronal injury and inflammatory reaction occur. This is due to the fact that there are differences in the susceptibility of nerve cells within the central nervous system Usually, the anterior horn cells in the enlargements of the spinal cord are most seriously involved, the large cells of this type being most severely damaged. However, the neurones of the posterior horn and the lateral columns are also affected In the medulla, lesions similar to those found in the cord are present, but the nerve cell damage is not so severe as that in the cord, and actual necrosis of the neurones in the basal ganglia has not been observed The motor nuclei of the 5th, 7th, 9th, 10th and 11th cranial nerves are particularly liable to injury, while the 3rd, 4th, 6th, and 12th are less often involved The reticular formation of the brain stem, the vestibular nuclei, and the roof nuclei of the cerebellum frequently show neuronal damage and inflammatory changes

The varying longitudinal extent in the spinal cord of the motor cell columns whose cells innervate individual muscles, may account for the characteristic distribution of muscle weakness in poliomyelitis For example, the quadriceps femoris, semimembranosus, semitendinosus, and gluteus maximus, which very frequently suffer partial paralysis, are supplied by long motor cell columns in the spinal cord Such long columns are more likely than short ones to be damaged in a portion of their length, but they are less liable to be destroyed completely Muscles such as the tibialis anticus and the tibialis posticus, are frequently paralyzed completely because they possess short motor cell columns which are

not interact to an important extent with the neuroglia, myelin, or blood vessels of the central nervous system *

The first changes are chromatolysis of some of the Nissl substance in the cytoplasm of some of the nerve cells and very mild inflammatory changes As the injury progresses the diffuse diminution in size of the Nissl bodies becomes more marked but the nucleus remains essentially normal In the next stage, there is almost complete chromatolysis of the Nissl substance and the chromatin of the nucleus becomes clumped As degeneration progresses, the cell becomes completely chromatolytic with acidophilic cytoplasm, and the nucleus becomes shrunken and completely distorted. Eventually, the cell is removed by phagocytic microglial cells (neuronophagia), and the neurones thus destroyed, are never replaced. The changes in the affected neurones may occur with great rapidity, some being destroyed in the pre-paralytic stage of the illness. On the other hand, many of the attacked cells do not undergo destruction The degenerative process may come to a halt in the stage of cytoplasmic chromatolysis and complete restoration of normal morphology then occurs within a month after the primary injury. It is clear from studies of animal as well as human material that some of the neurones injured by the poliovirus not only regain their normal morphologic appearance but actually recover their ability to function

Inflammatory changes never occur in the absence of nerve cell injury but severe neuronal chromatolytic degeneration may be found without accompanying inflammation or edema Thus, it may be concluded that neuronal injury is not due to the inflammatory reaction or to the edema which is sometimes present, but rather to primary damage caused by the virus. Polymorphonuclear and mononuclear leukocytes take part in the inflammatory reaction appearing first around the blood vessels (perivascular cuffing), and later such cells are found more diffusely in the gray matter. In the late stages of the

* Bodian, D. and Howe, H A Bull Johns Hopkins Hosp, 68, 58, 1941.

The symptoms of poliomyelitis affecting the central nervous system are explainable on the basis of the anatomical lesions found. Thus, loss of a skeletal muscle results from destruction of its motor neurone supply In some cases, the virus destroys practically all of the motor neurones of the spinal cord thus depriving the patient of nearly all voluntary muscle function Most of the time, however, effects of the disease tend to be spotty, the neurones of certain muscle groups and even those of entire extremities being spared It is a common experience, however, to find at autopsy that lesions in the cord are more widely spread than expected on the basis of the clinical findings

Since the neurones supplying innervation to a particular muscle are hundreds in number, and are usually situated in several segments of the cord, it is understandable that there may be permanent loss of merely a percentage of the neurones supplying a muscle Only temporary incapacity of another percentage may be present, thus, at least some spontaneous recovery is usual

Stiffness of the muscles of the neck and spine has been considered to be due to involvement of the meninges This explanation is probably not entirely correct because meningeal inflammation is not very pronounced in poliomyelitis It has been postulated instead that the rigidity of these muscles may be due to impairment of the central inhibitory mechanism caused by lesions in the subcortical centers in the reticular formation It has also been suggested that the generalized muscular spasticity and hyperreflexia often seen in the acute stage of poliomyelitis may be due to involvement of these neurones Tremor and ataxia which are observed in some cases, are probably due to involvement of the roof nuclei of the cerebellum Neuronal damage in the cerebral cortex is usually confined to the motor area of the precentral gyrus, and neuronal damage in this area is usually not severe and does not often produce clinical symptoms In a general way, the encephalitic symptoms such as restlessness, disorientation and coma are usually seen in cases showing the

likely to be obliterated totally by destruction of the cells in the relatively short segment of the cord containing them.* Similarly, the opponens muscle of the thumb is especially subject to complete loss of innervation.



FIG 67 —Poliomyelitis Section through an anterior horn of the spinal cord Loss of most of the motor cells (*A*)—one fairly well preserved nerve cell, (*B*)—damaged, pale nerve cell (chromatolysis), (*C*)—small microglial nodule, (*D*)—perivascular hemorrhage (From the collection of Dr. Vera B *Dolgopol*

* W J Sharrard, Poliomyelitis, Third International Poliomyelitis Conference, J B Lippincott Co , Philadelphia, 1955

mesenteric lymph nodes and lymph nodes in other areas and spleen The histologic changes in these organs are not different from those frequently seen in other infectious diseases, however, and their significance is not known

In a considerable proportion of fatal cases, the mucosa of the stomach and duodenum are intensely congested, and severe hemorrhages in the mucosa are found, with actual ulceration in some of the fatal bulbar cases

In the lungs atelectasis is often present, particularly in patients dying of respiratory difficulties. In some cases, the atelectatic areas are small, and patchy, while in others, segments and entire lobes may be affected In such cases pneumonia is common, and is usually bronchopneumonic in type. Pulmonary edema may be present in fatal bulbar cases Ordinarily, the edema is thin, and frothy but in some instances it is serous or even frankly bloody, large areas of the lung being engorged with blood The lungs of patients who die after long standing respiratory muscle weakness may show varying degrees of fibrosis and bronchiectasis.

Myocardial lesions are found at necropsy in approximately 15 per cent of patients dying of poliomyelitis These lesions cannot be distinguished from those produced in the heart muscle of human beings and animals by such agents as diphtheria toxin, and by vitamin and mineral deficiencies They are also similar to those produced by the Coxsackie viruses in the heart muscle of rodents The pathogenesis of the myocardial lesions found in poliomyelitis is not clear It seems very probable, however, that lack of oxygen caused by respiratory difficulties which are so common in severe cases of poliomyelitis contributes, at least to some degree, to the injury of the heart muscle fibers In addition, the systemic blood pressure is frequently elevated in severe cases of poliomyelitis and it is probable that the increased work required of the left ventricle contributes to the myocardial injury Finally, the possibility that poliomyelitis virus directly injures the myocardium cannot be excluded In fact, poliovirus has been isolated from human heart muscle in two

most severe reaction in the brain stem, and it is probable that these symptoms are not due to involvement of the cerebral cortex.

The nerve cells which control respiratory rate and rhythm may be affected when the medulla is involved The same is

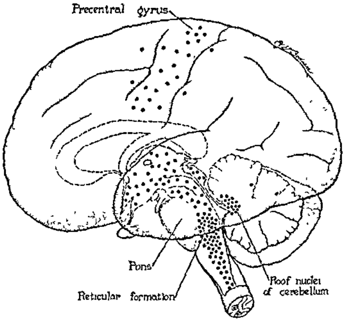


FIG. 68 —Lateral view of human brain, with schematic transparent pro-

Congress)

true of those medullary neurones which play an important part in the regulation of blood pressure.

Pathologic Changes in Other Organs.—Hypertrophy of lymph tissue is commonly found, including Peyer's patches,

development, and in fact in the very great majority of cases does stop at some early stage before paralysis occurs. Hence the rationale of the following classification of the types of infection becomes apparent.

1. **Inapparent Infection.**—Ninety to 95 per cent of those who come into contact with poliovirus remain entirely well, suffering no clinically detectable illness. Such individuals, however, develop antibodies against the virus, and as healthy carriers, they may excrete poliovirus in the stool for several days or even weeks. It is probable that the great majority of persons who become immune to poliomyelitis do so as a result of clinically inapparent infection.

2. **"Abortive Poliomyelitis" or Minor Illness.**—Four to eight per cent of patients who become infected with poliomyelitis experience symptoms of a systemic nature, without signs of involvement of the central nervous system at any time. This form of poliomyelitis has been termed "abortive poliomyelitis" or "minor illness." Fever, headache, sore throat, and gastrointestinal symptoms such as vomiting, diarrhea or constipation may occur. The illness lasts for only a few days, and clinical evidence of invasion of the central nervous system never appears, and the cerebrospinal fluid is normal. However, viremia occurs in at least a portion of these patients. They also excrete poliovirus in the stools, and antibody against the virus appears in the blood. Infections of the "abortive type" occur very frequently, particularly in members of families of paralytic cases and in their contacts, and a large portion of the population probably becomes immune to poliomyelitis in this way also. The diagnosis of "abortive poliomyelitis" can be strongly suspected in some circumstances, but it can be made with certainty only by laboratory means.

3. **Poliomyelitis Involving the Central Nervous System (Major Illness).** **A. Non-paralytic Type.**—In one to two per cent of poliovirus infections, symptoms of involvement of the central nervous system occur. In about half of this group of cases, the disease runs its course without causing clinically

cases which came to autopsy, while virus was not obtained from the blood of these patients

In patients who survive, the motor nerves coming from the destroyed anterior horn cells degenerate, and the muscles supplied by them become smaller in size. The tendons also atrophy, and even the bones undergo retardation of growth in children, and rarefaction and atrophy in full grown individuals.

The blood may show a slight increase in the total number of leukocytes but there is nothing characteristic in the total or differential counts

INCUBATION PERIOD OF POLIOMYELITIS

The incubation period in man probably falls within a period from four to thirty days, but is usually from seven to fourteen days

CLINICAL MANIFESTATIONS OF POLIOMYELITIS

A number of classifications of the clinical types of poliomyelitis have been proposed, some depending on the anatomical involvement, but a classification which is based on the possible course the disease may take will perhaps furnish the clearest understanding of the disease

A patient may first be taken ill with a mild systemic disturbance with upper respiratory and digestive manifestations, and may be ill for twenty-four to forty-eight hours This illness (often overlooked and more often absent) is probably a systemic reaction to the presence of the virus in the blood.

Following this minor illness, the patient apparently becomes well again, but after two to four more days, there may be a recurrence of fever and evidences of central nervous system involvement, due to invasion of the brain or of the cord by the virus. One to four days later paralysis may become evident. The disease may stop at any point in this

are occasionally reported, this manifestation at times being conspicuous enough to be mistaken for appendicitis Constipation is rather more common than diarrhea Retention of urine may last twenty-four hours or even up to seven days or more, occasionally requiring catheterization

Pain is a definite feature of acute poliomyelitis and appears in several forms, that is, (1) spontaneous, (2) on pressure, and (3) on motion. Even at complete rest many patients feel sore in various muscles, especially those in spasm, and have difficulty getting comfortable By palpation, muscle tenderness is usually found, often to a marked degree Pain is induced by any motion that stretches a muscle in spasm. In addition, some patients complain of cutaneous hyperesthesia. Sensory loss does not occur in poliomyelitis.

In appearance the patient looks and acts sicker than the degree of fever would indicate. The child may be drowsy, but when aroused he is irritable and wants to be left alone, because to be handled is uncomfortable if not actually painful *The face is flushed, the expression anxious, and there is* frequently pallor about the mouth The pharynx may be moderately congested

Vasomotor disturbances are common Sweating may be profuse, especially about the head Mottling of the general skin surface is frequent, and a *tache cérébrale* or reddish streak can at times be obtained in the skin of these patients by stroking them with a fingertip or other blunt point.

There may be coarse ataxic tremors especially of the hands, and when present they are of considerable prognostic significance. These are best demonstrated when a patient attempts to hold a glass of water at arm's length Twitchings or fasciculation of various groups of muscle fibers are occasionally present, and are said to indicate the site of future paralyses. Fasciculation is sometimes readily seen in the quadriceps in the anterior aspect of the thigh.

To make the diagnosis a careful physical examination for evidences of involvement of the central nervous system is usually necessary; but if the patient's general condition is

detectable muscle weakness or paralysis, and such cases are therefore called "non-paralytic." However, it is very probable that all patients who show clinical evidence of involvement of the central nervous system suffer some loss of neurone function, but in the "non-paralytic" patient, the portion of nerve supply which is injured is too small to cause detectable loss of muscle function. Furthermore, it is not *possible to determine whether a given case will turn out to* be a non-paralytic or a paralytic one until the disease has run its course, or at least until *the patient has been afebrile for* one or two days. Hence, a case believed to be non-paralytic in reality may be in the pre-paralytic phase which precedes the onset of muscle weakness or paralysis.

When the virus invades the central nervous system, the symptoms are quite specific in signifying progression from *constitutional manifestations to definite involvement of the* central nervous system. In most diagnosed cases of poliomyelitis, there is no recognizable stage of minor manifestations, but in some instances this stage has been present, and then after one to four days the temperature has risen again *with the appearance of manifestations of involvement of the* central nervous system, thus showing a two-hump fever curve.

With or without the preliminary involvement described as minor illness, the onset of symptoms of this new stage is usually rather sudden. Fever, headache, and vomiting are customarily the first symptoms. The temperature ordinarily rises to around 102° F., but may in some cases reach 104° F. or more. Fever persists for four or five days, or occasionally longer, even up *to eight days, and while it lasts there is* danger of the development of paralysis. The pulse-rate is usually *rapid* and out of *proportion to the fever*. Headache is occasionally very distressing, and may be general, occipital, or frontal, in type. In young children, this symptom is of special significance. Dizziness is occasionally present, and irritability is usual. Vomiting occurs in about one-half of the cases, and is commonly not persistent. Abdominal pains



FIG 70 —Illustrating tightness of the long posterior muscles of the neck preventing anterior flexion of the head on the chest despite the purposeful contraction of the sternocleidomastoid muscles (Courtesy of the National Foundation for Infantile Paralysis)



FIG 71 —Illustrating in contrast to Figure 70, normal flexion of the head on the chest (Courtesy of the National Foundation for Infantile Paralysis)

serious, or if the patient merely is very uncomfortable, a prolonged and detailed examination should be postponed until his condition has improved. Inspection alone can locate various shortened muscles, and gentle palpation and manipulation or passive motion can locate others If the patient is

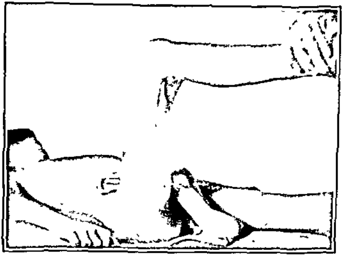
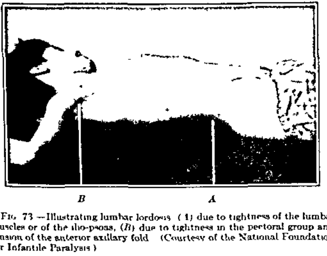


Fig 69 —Illustrating shortening of the hamstrings with tight tendons under the knee The Kernig position has relieved a lumbar lordosis (Courtesy of the National Foundation for Infantile Paralysis)

only slightly ill, active motion may be asked for and some of the most characteristic signs are found in the child's unwillingness or inability to bend the neck and spine When she is raised in bed to the sitting position, she holds her back stiffly, supports herself by bracing her hands behind her on the bed, and resists being bent forward when an attempt is made to have her head touch her knees (Fig. 72). The neck also is held rigid in order to prevent being flexed forward, but when the child is on her back there often is little or no opposition to rolling movements of the head. If the supine child is gently lifted by the shoulders, she allows her head to

The condition of muscle tightness found in acute poliomyelitis is variably known as spasm, spasticity, muscle shortening and increased muscle tension. The word spasm is not a satisfactory term for the condition to be described except that it is short and already rather widely known. To many it implies only a sudden or temporary cramp, but in poliomyelitis the term is used for two conditions. In the first place, there is increased shortening or tension of a muscle in its normal resting position. Secondly, there is



B *A*

FIG. 73.—Illustrating lumbar lordosis (*A*) due to tightness of the lumbar muscles or of the ilio-psoas, (*B*) due to tightness in the pectoral group and tension of the anterior axillary fold. (Courtesy of the National Foundation for Infantile Paralysis.)

hyperirritabilty of the stretch-reflex, or the so-called trigger mechanism. As an illustration, straight-leg raising beyond a certain angle at the hip, with the patient supine, causes a sudden painful contraction of the hamstrings, or literally a spasm.

In poliomyelitis, with or without loss of motor innervation, spasm, particularly in the form of increased muscle tension, furnishes an important cause of muscle dysfunction. It occurs in most recognizable cases of poliomyelitis, usually

drop back, sometimes because it hurts to hold the neck firm, sometimes because the anterior muscles of the neck are weak

The patellar and other deep tendon *reflexes* are occasionally exaggerated, and may be unequal, an important diagnostic point They disappear before or during the development of paralyses, which on the other hand are not likely to



FIG 72 —Showing the characteristic position which stiffness of the neck and spine causes a child to assume when asked to sit up in bed

develop in the absence of reflex changes. The cremasteric and abdominal reflexes are present during the first day or two but may also disappear, particularly in cases of paralysis of the lower extremities Kernig's sign is naturally positive when there is spasm of the hamstring muscles, but does not necessarily signify meningitis.

of spasm, even though this innervation may not be sufficient to cause an appreciable contraction of the muscle

There are several *causes* for increased muscle tension or spasm of which pain is the first Pain in poliomyelitis has several causes, but inflammation of the sensory roots of the cord is probably the predominating cause at least in the acute stage. Various pathological changes in the central nervous system also are considered responsible for spasm, such as damage of the internuncial neurones, and lesions in the subcortical centers in the reticular formation causing impairment of the central inhibitory mechanisms

In the presence of the various clinical manifestations described, particularly headache, tremor, and spasm of various muscles, especially of the neck, spine, and hamstrings, poliomyelitis affecting the nervous system should at least be suspected, and a lumbar puncture may be performed for further evidence for the diagnosis of the disease A blood count in poliomyelitis ordinarily shows a slight polymorphonuclear leukocytosis, but has no diagnostic or prognostic value.

The spinal fluid in poliomyelitis involving the nervous system, including the cases which prove to be non-paralytic, customarily shows an increase of pressure By the Ayer spinal fluid manometer, it may register 200 mm or more The fluid may be perfectly clear in cases where the cell count is low, or it may be slightly hazy, and occasionally it may develop the fine fibrin web appearance which occurs commonly [illegible]

ing also found at times in tuberculous meningitis, and in the early stages of a purulent meningitis. (See Table 11, p 407.)

The cells are, in the majority of cases, mostly mononuclears, the endothelioid type of cell being frequently found. During the first few days, polymorphonuclear cells may predominate The total number of cells averages from 200 to 300, but may vary from 5 to 1200 or more The number is

appearing shortly after the onset of fever and lasting only a few days in mild cases of the disease, but persisting up to many weeks, even months, in the more severe cases.

In the sense used, *spasm may be found* in the absence of any muscle weakness as in the neck, back, and hamstring muscles of non-paralytic cases. It may be found in muscles that also are partially weakened by loss of some innervation as in the intercostals of some patients with respiratory difficulty It also may be found in the opponents of weak-

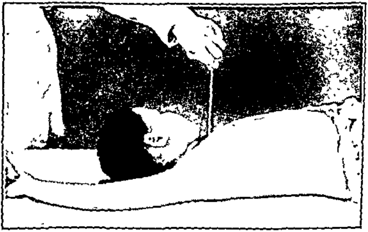


FIG 74 —Illustrating, in contrast to Figure 73, normal flatness of the lumbar region, and normal relaxation of the pectoral groups (Courtesy of the National Foundation for Infantile Paralysis)

ened muscles, as in the calf muscles when the anterior tibial is weakened Variable in its distribution, spasm is found in the neck, back, and hamstrings in most patients, but may be found in any other muscle group such as the pectorals, diaphragm, forearms, and calves

Spasm *originates* in the central nervous system rather than in muscle fibers themselves. Some intact neurones and persisting innervation of a muscle are essential for the production

the chances are about one in two or three that the patient will go on to develop definite weakness. However, a case should not be considered non-paralytic until the fever and all muscle tenderness and spasticity have subsided and until a careful muscle examination has then been made

B **Paralytic Type.**—The use of the word *paralysis* in connection with poliomyelitis must be guarded. If a muscle loses all its innervation as when a nerve is sectioned, there is complete flaccid paralysis. But in polio it is unusual for all the motor neurones innervating a particular muscle to be killed. Some may be killed and the particular muscle fibers they alone innervate are also killed Other neurones are injured and temporarily inactive, but in the course of several weeks they return to normal effectiveness Still others of the neurones remain more or less healthy and able to stimulate muscle fibers to contract unless voluntary contraction is interfered with by spasm or involuntary contraction

Thus, early in the acute stage the killed and the sick neurones are all ineffective and so-called paralysis is at its worst—may even seem to be complete in a given muscle Then as the sick neurones recover, more and more power is possible in a muscle, often amounting to normal efficiency even though some of the neurones and thereby some of the muscle fibers are killed.

During the period of waiting for recovery of innervation, spasm and pain may also cause a patient not to use a muscle Such pseudoparalysis occurs in many other conditions. A surgical patient whose fractured leg is put in a cast for weeks has to be taught again how to use his muscles. In poliomyelitis, after spasm and pain have gone, innervation may return to a muscle but without the patient's realization, and be rediscovered only when carefully sought after

Furthermore, during the period of dysfunction of a muscle the poliomyelitis patient is inclined to substitute some other group of muscles to perform the otherwise lost function He thereby develops faulty motor habits of substitution

usually at a maximum within the first three days with a tendency to fall after the fifth day, to reach normal by the tenth to fourteenth days The fluid is sterile and the presence in it of the virus has not been demonstrated. Albumin and globulin usually show a moderate increase which takes a day or two to appear but persists after the cell count returns to normal The amount of glucose is the same as in the normal fluid (60 to 80 mg. per 100 ml.) or it may be increased slightly above normal

The spinal fluid changes that are commonly found in poliomyelitis bear no relation to the presence or absence of paralysis, nor are they of prognostic value as to the likelihood of the occurrence of paralysis. On the other hand, they do not exist independent of definite pathology of the central nervous system whether or not clinical manifestations are present Exactly similar findings may be present in cases of encephalitis and lymphocytic choriomeningitis In exceptional cases of poliomyelitis, even at the height of the disease, a normal spinal fluid may be found Spinal fluid examination is of value in adding confirmation to the clinical impression of poliomyelitis because it differentiates between bacterial meningitis and viral infections of the central nervous system, including poliomyelitis

When recovery occurs without paralysis, doubt may be thrown upon the diagnosis of poliomyelitis That a non-paralytic type of the disease exists is proved by the following evidence. Virus obtained from the pharyngeal swabs of the noses and throats of patients of this type has produced typical poliomyelitis in monkeys The findings in spinal fluids from these cases are identical with findings in the fluids of patients with paralysis, and the serum from convalescent non-paralytic patients possesses the same specific neutralizing power as the serum from convalescent patients with paralysis

In the preparalytic stage, it is impossible to predict from the clinical symptoms, the physical findings, or the spinal fluid changes, whether the case will escape without paralysis or become paralyzed, or even go on to a fatal termination, but

jority of patients, very little recovery of muscle power occurs. Atrophy of the muscles which have been affected may start within the first ten days or two weeks after the illness begins. This atrophy, if the muscle remains paralyzed, tends to progress for a number of months.

The paralytic cases of poliomyelitis may be divided into the spinal, the bulbar, the cranial, and the encephalitic, with much overlapping of cases among several of these groups. Such overlapping is observed particularly in patients with respiratory difficulty, many of whom have both bulbar and spinal manifestations.

Spinal Cases.—The distribution and location of the paralyses vary considerably, but in the majority of paralytic cases one or both lower extremities are involved.

The muscles most commonly weakened in poliomyelitis are the anterior tibial, quadriceps, and hamstrings in the lower extremities, the deltoid, triceps, and thumb opponens in the upper extremities, the abdominal muscles, and the sternocleidomastoids, and in patients with breathing difficulties, the intercostals, the diaphragm, and the pectorals. Weakness is usually not symmetrical on the two sides and the pattern of paralysis, if any, follows nerve roots rather than nerve trunks. Only in rare cases are all four extremities more or less completely involved.

Particularly with leg weakness there is apt for several days to be an inability to empty the bladder, and some paralytic cases cannot voluntarily empty the bowel for two or three weeks or more. Exceptionally, bladder paralysis may be permanent.

When one deltoid is involved there often is some difficulty in breathing due to diaphragmatic weakness, the nuclei of the nerves innervating the deltoids and the diaphragm being close together in the cervical region of the spinal cord. When both deltoids show weakness, the diaphragm also is affected in nearly every case.

Bulbar Cases.—When there is evidence of involvement of the medulla oblongata or bulb, the clinical manifestations are

Thus "paralysis" in poliomyelitis is a complex condition of muscular dysfunction, the difficulty being due not only to more or less loss of innervation, but also to spasm, to pseudoparalysis, and to substitution

Weakness usually *appears on the second, third, fourth, or fifth* day of the disease, but may appear on the first day or on any day until even after the tenth day. In some cases it appears within a few hours of the onset of any signs of ill health, and may be preceded merely by lassitude and fatigue. Usually the paralysis reaches a maximum within a day or *two of its onset In some instances it appears to spread up the* body, in two or three days involving the muscles of respiration and causing death from asphyxia. In the average case, with the appearance of paralysis, the temperature gradually returns to normal in four to six days. Maintenance or increase of the fever is liable to indicate continued activity of the virus with possible extension of the paralysis It may indicate a secondary infection, however Backache and pain in the extremities may persist a number of days and muscle tenderness usually persists three or four weeks In cases in which the muscles of the extremities are affected, deep reflexes which have first been normal or increased, diminish and usually disappear before the paralytic stage Twitching may precede the paralysis in the affected muscle groups

Following the appearance of the wave of paralysis, recovery begins to set in Definite evidences of improvement may be found within two weeks. Some improvement can be expected in nearly every case, the greatest improvement occurring within the first three or four months after onset of the disease After this time, very little improvement occurs in the great majority of patients until the 8th or 10th month after onset At this time there is sometimes a second phase of returning muscle function less striking than that which occurred earlier, but which in many instances is nevertheless quite substantial. From this point on, improvement may progress slowly until 14 or 15 months after onset of paralysis and muscle weakness. Beyond this point, in the vast ma-

duration with a subsequent return to normal levels In some cases, unfortunately, hypertension is followed by a sudden fall of blood pressure, causing shock and collapse This sequence of events is a frequent cause of death in bulbar poliomyelitis

When neurones of the respiratory centers of the medulla are affected they lose their ability to respond to chemical and neurogenic stimuli and are therefore unable to initiate normal rhythmic respiratory movements An irregular, jerky pattern of breathing results, with periods of hyperventilation alternating with apneic episodes In such cases, the unaided patient cannot achieve continuous adequate pulmonary ventilation despite the fact that the diaphragm and other muscles of respiration which are innervated by neurones of the cervical spinal cord may be intact If the muscles of breathing are not also involved, such a patient may be able on command to take a single fairly good breath but unless helped, lapses into the semicoma of hypoxia

When the nuclei of the ninth to twelfth cranial nerves are affected, the patient loses to varying degrees his ability to swallow Saliva and mucus accumulate in the region of the epiglottis, interposing a barrier to the entrance of air into the larynx and trachea During inspiration, the accumulated secretions may be drawn into the trachea and bronchi Thus, loss of ability to swallow can in this manner cause serious obstruction to the respiratory tract and thereby can present one of the most serious threats to the life of the patient with bulbar poliomyelitis

Pulmonary edema may occur suddenly in patients with bulbar poliomyelitis, particularly when there is injury to the medullary autonomic centers which are associated with control of blood pressure There is also evidence that injury to the vagus nerve nucleus may be involved in the production of pulmonary edema It is believed that damage of these medullary neurones causes a constriction of the systemic vascular bed resulting in a transfer of blood to the pulmonary blood vessels This transfer brings about a rise in

due to the effect of the virus on the nuclei or the ninth, tenth, eleventh, and twelfth cranial nerves, and on the neurones which control the respiratory rate and rhythm, and those which regulate the cardiovascular apparatus and blood pressure, all of which are situated in the medulla. The other cranial nerves have their nuclei elsewhere The functions of the ninth, tenth, eleventh and twelfth cranial nerves overlap each other to such an extent that it is usually impossible to separate them In general they control the muscles of the palate, the pharynx, larynx, esophagus, and tongue. An early indication of bulbar involvement is regurgitation of fluids through the nose due to palatal weakness The voice becomes blurred or nasal in quality The gag reflex is lost, and the soft palate ceases to move Swallowing becomes difficult or impossible, and mucus and saliva accumulate in the pharynx, being secreted often in greater than normal quantities The tongue "gets in the way" and on protrusion deviates from the midline Coughing becomes difficult or impossible Because the act of coughing requires fixation of the diaphragm and a sudden contraction of the muscles of the anterior abdominal wall with the glottis momentarily closed, coughing is impossible either with laryngeal paralysis in bulbar cases, or with diaphragmatic or abdominal paralysis in spinal cases If the recurrent laryngeal nerve is involved with resulting paralysis of a vocal cord, there may be a change in the tone of the voice

Bulbar manifestations occur in 10 to 20 per cent of paralytic poliomyelitis patients in an epidemic The incidence of bulbar involvement is higher among adolescents and adults than it is is among younger individuals. Patients with bulbar poliomyelitis frequently have very high fever, and they are usually toxic and prostrated Their prognosis is especially grave, because of the danger of viral invasion of neurones of the cardio-vascular and respiratory control centers.

Evidences of damage of the medullary centers controlling blood pressure are manifested in the beginning at least, by the presence of hypertension This may be of short

since as stated in the section under Pathology, lesions in the cerebral cortex are almost entirely confined to the motor areas. It is very possible that such symptoms as coma, delirium, disorientation, hyperirritability and convulsions are in reality due to cerebral hypoxia rather than to lesions in the cerebrum. In fact, these symptoms often disappear when the oxygen content of the blood is increased by administration of oxygen or by artificial respiration. Further support of this idea is the fact that such "encephalitic" symptoms are most common in patients who are found at autopsy to have extreme involvement of the medulla. Such patients, of course, are most likely to suffer from hypoxia due to difficulties in respiration.

RESPIRATORY DIFFICULTY IN POLIOMYELITIS AND ITS TREATMENT

Poliomyelitis may cause difficulties in respiration in the following ways:

1. Viral invasion of the motor nerve cells in the central nervous system which activate the muscles of respiration (including the diaphragm, the intercostals and the accessory respiratory muscles), causes partial or complete loss of the muscular ability to expand and contract the chest.

2. The virus may injure the neurones in the medulla which control the rate, rhythm, and integration of the respiratory movements. The damaged neurones are unable to respond in the normal manner to changes in carbon dioxide concentration, pH and oxygen saturation of arterial blood. The respiratory movements are then incoordinated and irregular in depth and rhythm.

3. Obstruction to the respiratory tract may result from injury to the neurones which control the intrinsic muscles of the larynx and those which innervate the muscles of swallowing. These conditions may interfere directly with the entrance of air into the larynx and trachea, and secretions

the hydrostatic pressure in the pulmonary blood vessels to a degree sufficient to cause fluid to leak through them into the alveoli, thus causing pulmonary edema. Pulmonary edema is serious because it prevents the passage of oxygen across the fluid barrier in the alveoli, into the blood.

In some cases of bulbar poliomyelitis there appears to be evidence of myocardial damage, due to the action of the virus directly on the myocardium or it may result, at least in part, from the hypoxia which may be present in this form of the disease. At any rate, sudden cardiac enlargement, the appearance of murmurs, and a gallop rhythm, all point to cardiac involvement, as also do sudden enlargement of the liver, and such electrocardiographic changes as elevation of the S–T segment and depression of the T waves.

When bulbar cases survive, the various weaknesses of bulbar origin tend to improve rapidly and a large degree of recovery of function is the rule. The ability to swallow returns customarily within a week or ten days, and the soft palate is apt to regain essentially normal function early even though some weakness of one side or the other may persist. However, a small percentage of patients never do regain entirely normal swallowing capacity. In addition, a few patients remain hypertensive for years because of persistence of abnormal central blood pressure control.

Of the first eight cranial nerves, only the seventh or facial nerve is commonly involved. Weakness of the facial muscles may comprise the patient's only weakness, in which case the likelihood for complete recovery is good, or it may be part of a more generalized involvement. Weakness of the sixth nerve resulting in double vision is comparatively rare, and involvement of the other motor cranial nerves, the third, fourth, and part of the fifth, is even more unusual.

Encephalitic Cases.—Polio patients, particularly those with the bulbar form of the disease, sometimes exhibit symptoms which have been ascribed to the effect of the virus on the cerebral cortex. There is considerable doubt that these symptoms are in fact due to involvement of the cerebrum,

In attempting to estimate the condition of the respiratory muscles, the appearance of the patient is of utmost importance. The patient with even a mild degree of respiratory muscle weakness may appear anxious Restlessness, irritability, and wakefulness are present in varying degrees Respiration may not appear to be appreciably abnormal, or only a slight increase in rate may be noted With more serious weakness of the respiratory muscles, apprehension increases and the face becomes flushed As hypoxia and CO_2 retention increase, pallor replaces the florid appearance Respiration becomes rapid and labored and the use of accessory muscles of respiration and flaring of the alae nasi are noted Twitching of muscles such as those around the nostrils may be seen. Pulse and blood pressure rise, periods of cyanosis occur with increasing frequency Vasomotor collapse *with fall in blood pressure may occur suddenly* Coma, convulsions and death then rapidly ensue

Certain specific clinical and laboratory procedures have proved to be of great value in estimating severity of breathing difficulty The strength of the intercostal muscles is tested by having the patient expand the chest against manual pressure exerted against the lower portion of the rib cage. The intercostal muscles are also tested by restriction of diaphragmatic excursion by pressure applied to the upper portion of the abdomen Since sniffing is brought about entirely by descent of the diaphragm, ability to carry out this action constitutes an excellent test of diaphragmatic function The resting small child with normal breathing ability is able to hold his breath for 15 to 20 seconds, the child suffering from respiratory muscle impairment of relatively slight degree falls far short of this When a stethoscope is placed over the open mouth of a normal child, a loud, sustained rush of air is heard on exhalation. There is noted a decrease in volume and duration of the expiratory sound in children with impaired breathing.

The function of the respiratory muscles can best be judged by these clinical considerations, but certain laboratory aids

which accumulate in the pharynx may be aspirated into the bronchial tree, further blocking the passage of air.

4. When bulbar disease is present, pulmonary edema may occur as a result of injury to the medullary autonomic centers which control blood pressure, as described in the section on the pathogenesis of bulbar poliomyelitis. Presence of the fluid in the alveoli obviously interferes with the diffusion of oxygen from the bronchioles to the capillaries in the alveolar walls.

In many cases a number of these difficulties coexist. In the following pages these four factors are discussed in detail, together with their treatment.

Certain secondary factors may increase the patient's respiratory difficulties. These include fever, fatigue, anemia, air swallowing and abdominal distention from any other cause.

In addition to these physical causes of respiratory difficulty, there are psychological factors which may add to the patient's problems. Fear, panic, and hysteria may provide an added handicap to breathing which may make artificial respiration necessary. Anxiety may be accompanied by shallow, rapid respiratory movements which are relatively inefficient, and increase the work of the respiratory muscles.

It is possible that during the acute stage of the disease, tightness of the intercostal muscles and the abdominal muscles may interfere with respiratory movements. In most cases, however, this is not an important factor.

1 Breathing Difficulties Due to Weakness of the Muscles of Respiration and Their Treatment

Loss of function of the muscles of respiration may be of such slight degree that interference with breathing is scarcely detectable. In other instances, the loss may be of such magnitude that practically complete paralysis of all muscles groups involved in respiration is apparent.

In attempting to estimate the condition of the respiratory muscles, the appearance of the patient is of utmost importance. The patient with even a mild degree of respiratory muscle weakness may appear anxious. Restlessness, irritability, and wakefulness are present in varying degrees. Respiration may not appear to be appreciably abnormal, or only a slight increase in rate may be noted. With more serious weakness of the respiratory muscles, apprehension increases and the face becomes flushed. As hypoxia and CO_2 retention increase, pallor replaces the florid appearance. Respiration becomes rapid and labored and the use of accessory muscles of respiration and flaring of the alae nasi are noted. Twitching of muscles such as those around the nostrils may be seen. Pulse and blood pressure rise, periods of cyanosis occur with increasing frequency. Vasomotor collapse with fall in blood pressure may occur suddenly. Coma, convulsions and death then rapidly ensue.

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may be of value Fluoroscopic examination is often of great value It may reveal a decrease in the diaphragmatic excursion, a lag of one side of the diaphragm or a paradoxical movement Fluoroscopy may help to distinguish between respiratory center disease and diaphragmatic weakness. In the former, irregular movement of the diaphragm will be seen, while in the case of diaphragmatic paralysis, movements are limited but regular.

A spirometer of the type used to measure basal metabolism is of use to estimate the state of pulmonary ventilation The most valuable spirometric measurements from a practical standpoint is that of the vital capacity. Patients with falling vital capacities demand very careful watching In a general way, when the vital capacity of a patient in the acute stage of poliomyelitis falls to a point below 33 per cent of his expected minimum value, artificial respiratory assistance is usually needed

A constantly rising CO_2 content of venous blood usually indicates severe underventilation

Treatment of Respiratory Muscle Weakness.—The respiratory muscles normally enjoy a large functional reserve When poliomyelitis causes only a small loss of function, the muscle reserve will be able to meet respiratory needs Only a slight increase in respiratory rate will occur and no evidence of distress or effort will be noted. These patients will need no mechanical aid to respiration.

In some patients the respiratory muscles are so impaired that conscious effort is necessary to supplement their action. If this effort at compensation is successful, mechanical aids need not be employed For example, the respiratory effort of such patients might be relieved sufficiently by the administration of oxygen to enable them to obtain rest and sleep. However, if there is evidence that compensation is not adequate, then mechanical help is necessary. When the patient's effort to maintain adequate pulmonary ventilation interferes with sleep, mechanical aid to respiration is required, despite the disadvantages in the use of all types of

apparatus available for aiding respiration. It is a grave mistake to postpone mechanical therapy until the appearance of the signs of hypoxia or of CO_2 accumulation, which are evidence of respiratory decompensation.

The decision regarding when to use mechanical therapy should also be influenced by the general condition of the pa-

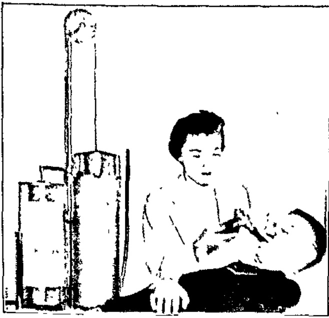


FIG. 75. Testing vital capacity and tidal volume with a basal metabolism recording spirometer. Each vertical millimeter on the graph is equivalent to 20.7 milliliters of air in this particular tank. In this patient vital capacity is recorded as 650 ml. and tidal volume as 150 ml., approximately.

tient. With a given degree of respiratory muscle weakness, the patient who is afebrile and who shows no evidence of advancing paralysis of other muscle groups may require no treatment, while the febrile patient who shows evidence of increasing paralysis may need such aid. Similarly, a very

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least traumatic and simplest to operate. When relatively minor degrees of respiratory muscle weakness exist, the cuirass respirator or the rocking bed may be employed to give rest and sleep. In general, however, both these latter machines are of greatest usefulness in the recovery period and in weaning patients from the tank respirator. Positive pressure devices applied to the mouth and nose or to a tracheotomy tube are not suited for prolonged use but are probably most valuable as an adjuvant for the tank respirator. The electrophrenic respirator is not suited for treatment of loss of function of the respiratory muscles, its main use is in the treatment of respiratory impairment due to injury to the respiratory center. Manual methods of artificial respiration are important since sometimes they are the only means available. However, they are temporary emergency methods only.

The Tank Respirator.—The modern tank respirator operates by alternately increasing and decreasing its volume by means of a bellows. The patient's body lies within the tank, the head outside it. A flexible rubber collar around the neck acts as a seal. The head, nose, and throat remain always at atmospheric pressure. When the bellows of the respirator opens and thereby increases the tank volume, the body, including the thorax and abdomen, is subjected to a decrease in pressure below that of the atmosphere, and air is forced into the lungs by atmospheric pressure on the nose and mouth. When the bellows of the respirator folds up, the tank volume is decreased and the difference in pressure between the inside of the chest in the tank and that of the atmosphere disappears. The elastic recoil of the thorax accomplishes the expiratory phase of respiration.

A respirator should never be used if obstruction to the airway is the only cause of respiratory difficulty. However, such obstruction may coexist with loss of power of the respiratory muscles which is so severe that the use of the respirator is required. In this case, the obstruction to the airway must be removed before placing the patient in the

sick patient may be incapable of the effort required to compensate for respiratory muscle weakness, while a patient in good general condition with a similar loss of respiratory muscle power may easily make a satisfactory adjustment

In the use of mechanical aids to respiration, a general principle is that the patient's possible needs must always be anticipated, and unexpected crises should be avoided A second general principle of utmost importance is that the psychological factors involved in the use of artificial breathing devices must be recognized and treated The patient with respiratory difficulty is, with reason, apprehensive and anxious. The physician must do everything in his power to allay these anxieties He should explain the objectives of a respirator, lay emphasis upon its beneficial effects, its temporary nature, and the usually successful outcome If patients are nearby who have come through a period of respirator treatment, they should be cited as examples The patient's parents should be acquainted with the same factors and, if their influence might be beneficial, their assistance should be employed The aid of a psychiatrist, if available, should be employed throughout the patient's illness.

The aim of mechanical therapy is to replace or to supplement the inadequate respiratory motor mechanism The method is basically simple—the rhythmic creation of a pressure difference between the alveolar spaces and the outside of the thorax sufficient to distend the lungs by the desired amount The pressure difference on which inflation depends may be created by increasing intra-pulmonary pressure by the intermittent application of positive pressure to the upper airway, as in "positive pressure breathing," or expansion of the chest may be produced by reducing pressure around the body, as occurs in the tank respirator and in the cuirass respirator Both methods bring about the same physiologic results.

Choice of Respirator—For all-round usefulness in the treatment of severe degrees of respiratory muscle weakness, the tank respirator is the apparatus of choice in that it is the

intratank pressure ranging from 0 to −12 cm. of water is suggested for the beginning. For adults, a range of 0 to −18 cm. may be tried. Some workers employ pressures which range from a positive reading of + 3 or + 5 to − 18, as indicated in Table 13. These ranges of settings are offered merely as a starting point. Initial pressure and rate then should be altered until evidence of improvement is noted.

TABLE 13.—SUGGESTED RANGE OF SETTINGS FOR TANK RESPIRATOR

Age	*Rate per Minute*	*Pressure*
0 to 2	30	Minus 12 to plus 3
2 to 10	24	Minus 15 to plus 5
10 to 15	20	Minus 15 to plus 5
Adult	18	Minus 15 or minus 18 to plus 5

These signs include:

1. Improvement in, or disappearance of, symptoms of hypoxia such as restlessness, pallor or cyanosis.

2. Acceptance of rhythm of respirator and cessation of voluntary respiratory movements, or synchronization of these movements with the respirator. The use of accessory muscles of respiration usually stops.

3. Disappearance of anxious facial expression. Patient often relaxes, dozes and may fall asleep.

No single consideration will determine the correct rate and pressure range. Clinical observation of the patient's condition is the best guide. A course must be steered between underventilation and hyperventilation, but hyperventilation is by far the lesser danger. Estimation of the patient's "minute volume" obtained with the spirometer is a rough index of the adequacy of ventilation. However, the value of this measurement is limited and must be considered together with the clinical findings. The data in Table 14 represent normal figures. The minute volume required in the presence of fever is much higher.

The state of the patient's circulatory system may have a bearing on the pressures used. The respirator is a positive

respirator If the obstruction is due to accumulation of oral secretions or to abductor paralysis of the vocal cords, tracheotomy is usually required. *Consideration of the treatment* of obstruction of the respiratory tract is given on page 496.

In most instances the need for the use of the respirator will have been anticipated so that everything should be in readiness The patient should be prepared from the psychological standpoint. The attendants should move and act with calmness and assurance They must be familiar with the respirator they are using and they must be able to make any adjustments which may be necessary They themselves should have had the experience of being put in a respirator for a brief period. Electricians and mechanics should be at hand for making repairs Spare parts should be immediately available, particularly a variety in sizes of collars.

When the moment for placing the patient in the respirator is reached, an old, soft diaper, folded once lengthwise, is placed around the patient's neck. After the stretcher of the respirator is pulled out, the patient is lifted gently onto it His head is then drawn through the collar, care being taken not to injure the nose, chin and forehead in this procedure. The arms are arranged comfortably, with elbows close to the patient's body, in order to avoid injuring them when the stretcher is pushed back into the respirator shell The legs are also arranged in as comfortable a manner as possible *Generally, a pillow beneath the knees is desirable* The collar is adjusted to the patient's neck and gaps between the neck and the collar are filled with soft cotton batting The rubber of the collar should not touch the skin anywhere The switch is turned on and the stretcher pushed into the tank All clamps and ports are closed, and rate and pressure range adjustment is begun

In general, younger children are given a more rapid respiratory rate than older children or adults They are also subjected to smaller pressure ranges than adults, although some competent and experienced physicians do not follow this practice. In using the tank respirator for small children,

washing and by the use of alcohol-containing lotions At no point should the rubber of the collar touch the skin It is better that the collar leak a little air than that it be tight enough to cause venous congestion of the head.

Weak extremities should be arranged in the most comfortable position and the position of the trunk and head should be changed frequently The precaution used to prevent foot drop when patients are in bed should be employed for respirator patients

Attention should be paid to the temperature within the respirator, which in mid-summer may be very high and may cause great discomfort. Excessive sweating and irritation of the skin may contribute to the patient's distress. The respirator may be cooled by placing in it pans containing CO_2 snow. A cooling effect may also be obtained by a small electric fan so placed within the respirator that it directs a stream of air upon a basin containing a block of ice.

Physical therapy should not be attempted during the period when fever is present and it should certainly be postponed until satisfactory adjustment to the respirator has been made This treatment should be carried out under the same principles which guide its use for the non-respirator patient A serious attempt should be made to overcome the limitations imposed by the respirator in this regard Physical therapy should not, of course, interfere with the fulfillment of the patient's respiratory needs, but a great deal can be done through the ports of the respirator. When the breathing status improves, precedures may be carried out with the patient on the respirator stretcher which has been pulled out of the tank In this situation the positive pressure dome or a chest respirator may be used

During the period of complete dependence upon the machine, necessary nursing care, such as bathing, use of bedpan, and taking of temperature, are carried out through the ports in the tank Later, when the patient is able to remain out of the respirator, some of these procedures may be carried out while the patient is on the stretcher of the machine

pressure device for artificial respiration and it therefore interferes with the venous return to the right atrium The normal response to this change is a rise in the peripheral venous pressure and reestablishment of the venous return to the heart. When shock is present, this response may not occur Therefore, when blood pressure is low, positive intra-tank pressure should be used in the same cycle with negative intra-tank pressure to give a mean pressure only slightly above atmospheric. By this technic, venous return to the right atrium will be increased and cardiac output improved

TABLE 14 —NORMAL MINUTE VOLUMES

	Age (years)	*Average MV (resting)*	*Range of Normal*
Male	5-14	5 9 L/min/M^2	4 3-7 6 L/min/M^2
	16 34	3 6	3 1-4 5
Female	5 14	5 9 L/min/M^2	4 3 7 6 L/min/M^2
	16 34	3 2	2 6-4 3

Minute volume is the total volume of air inspired in one minute, it is measured with a spirometer Normal minute volume is calculated in liters of air per square meter of body surface area (M^2)

When breathing difficulty is due entirely to weakness of the respiratory muscles, the tank respirator is of very great benefit When improvement is not obtained quickly, complicating factors must be sought, such as obstruction to the airway, pulmonary atelectasis, pneumonia and pulmonary edema

Care of the Patient in Tank Respirator.—Every effort should be made to promote the patient's comfort. Great care should be exercised to prevent irritation and bruising of the skin by the respirator collar. This is best accomplished by carefully folding the padding around the neck, by adjusting the collar so that it is not too tight around the neck, and by keeping the skin in good condition by frequent, gentle

the required fluid volume may be given as a solution of 5 per cent dextrose in 0.85 per cent NaCl, alternating with 5 per cent dextrose in distilled water. Protein, mineral, vitamin, and caloric requirements should be estimated and a vigorous attempt to meet them should be made. Such proprietary preparations as Sustogen* are of value for gavage feeding.

Weaning from the Tank Respirator.—When the intercostals and diaphragm are weak or paralyzed, the chest tends to assume a greater diameter than normal and the lungs tend to contain more than the normal volume of residual air, as occurs in the emphysema which is present in chronic asthmatic patients. This results in an increase in the residual lung volume and consequent loss of tidal volume and inspiratory reserve. Patients who have been in a respirator for a prolonged period usually show these changes and it is believed that the fixation of the chest in the emphysematous pattern may also be due to changes in the thoracic muscles as well as in the ligaments around the rib-vertebral articulations. Some of these changes may be avoided if removal from the respirator is accomplished as early as is safely possible. Thereby, the percentage of persons who become chronic respirator patients will be decreased. Hence, when the patient is afebrile and is able to do without the respirator for 30 to 60 seconds, weaning is started. The tank respirator may be gradually replaced by less efficient devices—the cuirass respirator and the rocking bed. This step forces the patient to employ his own muscle power to the fullest extent. The weaning process must be carried out slowly and carefully, and fatigue and fright must be avoided.

The Rocking Bed.—This apparatus is a mechanization of the Eve tilting board method of artificial respiration. When the foot of the bed rises, the movement of the abdominal viscera against the diaphragm causes compression of the lungs. When the foot of the bed is depressed, movement of the abdominal viscera away from the diaphragm occurs and reexpansion of the lungs takes place. Fairly effective ventilation can be achieved by this method. A number of rocking

In general, it is a good principle as far as possible to avoid disturbing the patient during the period of adjustment to the respirator. Fever, pain and tenderness of muscles also require that handling be reduced to a minimum in the early stages. On the other hand, proper bathing, care of the skin and maintenance of nutrition are of the same importance here as in the treatment of typhoid fever Therefore, as soon as the patient's condition warrants, these measures are given an important place in the treatment regimen. Pressure sores are prevented by proper protection of bony prominences, with padding, air cushions, or other soft materials. Frequent bathing and application of lotions and powder to the skin are essential. Most important in this regard is the frequent changing of the patient's position in the tank

During the first 8 or ten hours after the patient is placed in the respirator, feeding should be omitted After this, small sips of water only are given until it is clear that the patient is able to swallow while the respirator is in action. Liquid foods are then given, and when fever has subsided, soft foods Later, solid foods can be given. Often meals can be scheduled during the patient's periods out of the respirator

During the acute stage, fever increases the patient's need for fluid. Hot summer weather and the heat within the tank respirator contribute to the loss of water A decrease in body water is in general harmful to patients with infectious diseases In the case of the polio patient with extensive paralysis, there exists a tendency to hypercalcemia due to extensive demineralization of bone In conjunction with decreased output of urine, this may lead to the formation of calculi in the urinary tract. It is therefore doubly important to maintain a normal state of hydration in these patients. The blood hematocrit determination may be used as a rough guide in this regard, the higher the hematocrit reading the greater the degree of dehydration. Since it is often not possible for the patient to drink the required amount of fluid, intravenous therapy may be necessary. In general,

proportion of breathing ability has returned. In this phase of the disease, it may be employed alone or alternately with the cuirass, or with the tank respirator, or both

The Cuirass Respirator.—This apparatus consists of a shell which fits closely around the anterior portion of the thorax and most of the abdomen. The shell is attached to a pump and valve device which alternately decreases the pressure within the shell, and permits it to return to the atmospheric level There is thus produced a movement of air into and out of the lungs in a manner similar to that of the tank respirator. It is not possible to achieve so large a degree of pulmonary ventilation with the cuirass as with the tank respirator, but the cuirass is more effective than the rocking bed Like this latter, the cuirass respirator is not used in the treatment of the acute stage of severe respiratory muscle paralysis, but is effective in patients with a small loss of respiratory capacity. Its greatest use, however, is in weaning from the tank respirator and in the treatment of patients with improving respiratory ability, also for use during the transportation of most patients needing help to breathe

Glosso-pharyngeal Breathing ("Frog Breathing").—Some patients with respiratory muscle weakness have learned to keep the epiglottis open while making swallowing movements, thereby forcing air into the lungs By repeating this process many times before exhaling, effective pulmonary ventilation can be achieved This form of breathing has been named "frog breathing." Although it requires a conscious effort, with practice frog breathing can be carried out for hours Frog breathing furnishes the patient with an important safety factor which can tide him over a period of failure of his mechanical respiratory devices In addition, frog breathing furnishes a large volume of air which is of assistance in coughing, in speaking, or calling aloud in case of emergency For these reasons, all persons with severe impairment of respiratory function should be encouraged to try to learn frog breathing

beds are available which permit a wide range of rate and angle of declination.

The efficiency of a rocking bed is diminished if the patient has a flaccid diaphragm, or distention of stomach or bowel, or weak abdominal muscles unless supported by a belt with abdominal pad. One young mother on a rocking bed found she could breathe better if her baby was lying on her ab-

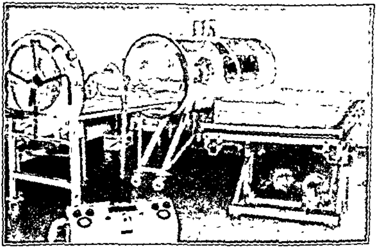


FIG 76 —Showing tank respirator, cuirass respirator (in use) and rocking bed

domen In addition, in order not to handicap the breathing further, the head should not be flexed on the chest nor the body flexed by raising the gatch markedly The patient's feet should rest on a foot board

The rocking bed does not produce a sufficient degree of pulmonary ventilation to be used in the acute stage of severe respiratory muscle weakness. However, this apparatus can be used to assist the breathing of patients with less severe degrees of such weakness. The rocking bed is of greatest usefulness in weaning the patient from the tank respirator, and in treatment during convalescence, when an appreciable

the function of an entire lobe or lung may be lost. On occasion a single aspiration of a large quantity of fluid may lead to sudden fatal asphyxia.

Difficulty in swallowing should be suspected when there is an unusual amount of spitting, drooling or hacking. Continual and noisy clearing of the throat, and gurgling and bubbling sounds coincident with respiratory rhythm are also significant findings. The patient's respiratory rhythm may assume a bizarre pattern as he attempts to hold his breath until he ejects accumulated saliva. On examination of the throat, the pooled saliva and mucus will be seen. Normally, when the patient is asked to say "ah," the lateral pillars of the pharynx should move toward the midline. When weakness of the pharyngeal muscles is present, this movement may not occur.

Paralysis of the uvula, palate, facial and oculomotor muscles and masticating muscles do not *per se* interfere with respiration. They are, however, indications of involvement of the bulb and should therefore be carefully sought. Evidence of palatal paralysis causes (1) inability to raise the palate when an attempt to say "ah" is made, (2) loss of gag reflex, (3) nasal quality of the voice, (4) regurgitation of fluid through the nose. Facial, abducens, and oculomotor nerve functions are tested in the familiar manner. The masseter is tested by having the patient bite on a tongue blade. If the blade can readily be withdrawn, weakness of the masseter exists. The tongue is not often paralyzed in polio, but when it is weakened on both sides, it tends to fall back in the mouth if the patient is supine and may interfere markedly in breathing. Relief follows turning the patient face down, or at least on his side.

Obstruction of the airway may occur at the level of the larynx. This may be due to aspiration of a foreign body (food) into the larynx when difficulty in swallowing exists or it may be due to apposition of the vocal cords resulting from paralysis of the abductor muscles. Neither of these factors is so common a cause of respiratory tract obstruction in

2. Breathing Difficulties Due to Injury of Medullary Respiratory Centers

When neurones of the respiratory centers are affected, they lose their ability to respond to chemical and neurogenic stimuli to initiate normal, rhythmic respiratory movements. An irregular, jerky pattern of respiration results. Periods of hyperventilation may alternate with apneic episodes. Often signs are present of injury to other medullary centers such as those controlling blood pressure, and cranial nerve weaknesses are common. If there is no involvement of the usual muscles of breathing, these patients can often take one or two good voluntary breaths on command.

Patients with disease of the respiratory centers nearly always require mechanical aid to respiration. The tank respirator may be used, but lack of synchronization usually decreases its efficiency. Nevertheless, the machine nearly always effectively increases the minute volume. If the tank respirator fails, the electrophrenic respirator is used to cause respiration by rhythmic stimulation of a phrenic nerve to contract the diaphragm. This apparatus is effective because it immediately stops all irregular spontaneous respiration. However, certain limitations of this apparatus lessen its usefulness.

3. Respiratory Difficulties Caused by Obstruction of the Airway

Loss of ability to swallow is the most common cause of respiratory tract obstruction. It is caused by disease of the ninth, the tenth, and the eleventh cranial nerves. Saliva and mucus accumulate in the region of the epiglottis. This interposes a barrier to the entrance of air into the larynx and the trachea, and during inspiration the pooled secretions may be drawn into the trachea and the bronchi. The result of this aspiration varies with the quantity and nature of the material aspirated. A small bronchus may be occluded or



FIG 77 —"The bulbar position" A proper position for a patient unable to swallow but without breathing difficulty The head is in line with the spine The veins in the right elbow and on the dorsum of the left hand are accessible for infusions A large pillow against the back and another between the knees are for comfort The moderate elevation of the foot of the bed with shock blocks is not shown

poliomyelitis as is loss of ability to swallow Choking due to aspiration of food is usually promptly relieved by turning the patient prone and head down and patting him on the back.

Paralysis *of the abductor muscles of the larynx causes* aphonia, stridor, dyspnea and retraction of the sternum The patient rapidly becomes worse and symptoms and signs of severe anoxia may develop rapidly Laryngoscopy will establish the diagnosis beyond doubt. Obstruction caused by paralysis of the abductor muscles of the larynx requires immediate tracheotomy

The general principle of treatment of obstruction caused by inability to swallow, is to provide a constant free airway by postural drainage and mechanical aspiration of the secretions in the pharynx. If this fails, tracheotomy is performed *to provide an airway which is much less susceptible to obstruction.*

The patient who can not swallow should be kept in the position which is the most effective protection against aspiration This position is one in which the head is lower than the feet and a face-down position is safer than one in which the patient is on his back The greater the elevation of the feet, the less the danger of aspiration, but there are practical limits to the angle at which the patient can be maintained An angle over 15 degrees from the horizontal increases intracranial pressure and often causes headache and edema of the face. An angle of 10 to 12 degrees is best. Unfortunately, the patient is often less comfortable in a face-down position than he is when lying on the side However, the face down and the side position may be alternated. Figure 77 shows one position which has been found very satisfactory.

There are a number of effective mechanical means for removing secretions from the pharynx The catheter is connected to a mechanical device which produces intermittent or constant suction. An electrically driven suction machine or a thermotic pump may be used. In general, a negative

of aspiration alone Tracheotomy is also considered necessary if the constant accumulation of secretions and the attempts at their removal prevent rest and sleep, and appear to be causing definite harm for this reason A cooperative patient is less likely to require tracheotomy than a panic-striken one, and adults and older children are less likely to need it than very young children

Mechanical respiration is obviously dangerous in the presence of respiratory tract obstruction. However, patients with pharyngeal paralysis may also suffer paralysis of the respiratory muscles, and therefore may require treatment in the tank respirator. In this situation, there is great danger of aspiration, and tracheotomy must be done, usually before artificial respiration is started

For the feeding of patients with bulbar poliomyelitis, see page 515

4 Breathing Difficulties Caused by Pulmonary Edema

Pulmonary edema, as stated above in the discussion of bulbar poliomyelitis (p. 479), may occur in patients with that form of the disease It may develop suddenly and is often a terminal event The alveolar fluid may be thin and frothy but in many cases coming to autopsy, the edema fluid is serosanguineous or sometimes bloody.

The chief defect caused by pulmonary edema is that the fluid in the alveoli interferes with absorption of oxygen into the blood. This condition also decreases pulmonary compliance (elasticity).

Oxygen therapy should be given to increase the concentration of this gas in the alveoli and to favor its passage across the fluid barrier into the blood Positive pressure breathing also should be instituted It may be applied by increasing the negative intra-tank pressure if the patient is in a respirator or by giving oxygen under pressure by mask over the nose and mouth, or by applying it to the tracheotomy tube. This increases lung volume and produces thinning of

pressure of 10 to 12 cm. of water is used. The thermotic pump, providing gentle intermittent suction, is very useful in most cases, but it sometimes fails to remove thick secretions Despite the more or less constant suction provided by the method described, most patients with serious pharyngeal weakness require additional assistance. This must be provided by a trained person who must be in constant at-

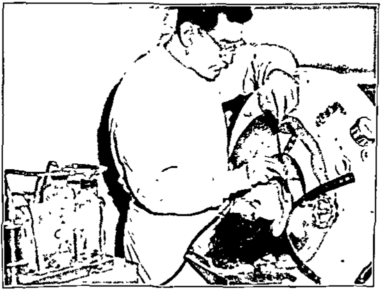


FIG. 78 —Showing care of patient with tracheotomy in tank respirator Note retraction of respirator collar by metal bar

tendance, ready to use an auxiliary suction apparatus equipped with a curved metal tube (or a flexible suction tube) which is passed through the mouth into the pharynx. This type of aspiration, with practice, can be performed gently and swiftly. In the presence of weakness of the muscles of swallowing, each case must be carefully judged and tracheotomy is done if it is believed that it will be impossible to guarantee that the airway will remain unobstructed by means

When the respiratory centers have been damaged, they exhibit a reduced sensitivity to a rise in the carbon dioxide tension of arterial blood. In this situation, the respiratory centers do not respond to a rising CO_2 concentration of the blood, the only stimulus to which they do respond being a

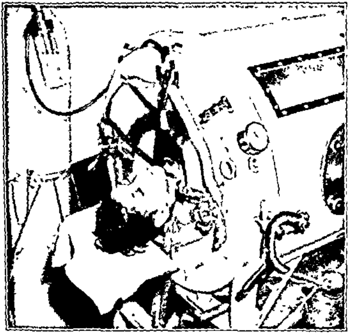


FIG 79 — Administration of oxygen to patient with tracheotomy in tank respirator, using a narrow funnel hanging over the opening Note bottle in which oxygen is passing through warm water

reduction of arterial oxygen saturation. Therefore, if hypoxia is relieved by administration of oxygen, it is possible to abolish auto-respiratory movements entirely, since the last stimulus to which the respiratory centers react has been removed This consideration does not hold when the patient is receiving some form of artificial respiration, but it is

the layer of fluid in the alveoli, thereby aiding gaseous diffusion Positive pressure may be of value also because it reduces the venous return to the heart and thereby decreases the work of the left ventricle.

When cardiac insufficiency is present, digitalis and other measures to improve cardiac function are indicated. Since constriction of the systemic blood vessels is believed to play a major role in the production of pulmonary edema, the use of vasodilating drugs seems logical. However, experience with such drugs is too limited at present to permit making an estimate of their value

Oxygen Therapy in Treatment of Respiratory Difficulty Due to Poliomyelitis

Oxygen therapy is clearly indicated when there is an increased barrier to the diffusion of oxygen from the lungs into the blood, such as occurs when pulmonary edema is present It is also needed when a significant amount of blood flows through unventilated lung, such as is present when pneumonia or atelectasis complicate poliomyelitis Oxygen therapy may also be helpful when the lung is being underventilated as a result of weakness of the respiratory muscles or of injury of the medullary respiratory centers However, when the patient is in the tank respirator, lung ventilation can be effectively increased by widening the pressure range of the respirator. In general, after the patient has adjusted to the respirator, oxygen will not be necessary unless a complication such as pneumonia, atelectasis or pulmonary edema is present. However, after it has been judged that the tank respirator is functioning at the optimal pressure range and if hypoxia is still considered to be present, oxygen therapy should be given a trial but relieving hypoxia may still leave the patient with an excess of carbon dioxide in his blood as a result of hypoventilation The only adequate treatment for inadequate pulmonary ventilation is to improve the aeration of the lung by increasing respiration.

ment. When atelectasis is present, dyspnea may be seen and there may be retraction at the sternal notch. Differences in expansion of the chest due to the collapse of portions of the lung may be observed. Dislocation of a palpable apex beat, and auscultation and percussion may reveal the heart to be displaced toward the side of a collapsed lobe or lung. Rales and squeaks indicative of fluid in the trachea and bronchi may be heard. Fluoroscopic examination will give a fairly clear picture of the extent of atelectasis. The symptoms of anoxia and CO_2 retention may be present. Cyanosis, periods of apnea, convulsions, unconsciousness and death may result if relief is not afforded.

Prevention of atelectasis is best accomplished by obtaining maximum lung ventilation, by preventing aspiration, and by prompt and thorough removal of aspirated materials. Changing position of the patient in the respirator may also be of value, since the expansion of areas of the lungs which are dependent may be improved in this way. Drainage of bronchial secretions may also be improved by changes in position.

When the presence of atelectasis is detected, antibiotics should be used to prevent pneumonia, and as soon as possible, the mechanical steps needed to reexpand the collapsed portion of the lung should be instituted. Oxygen therapy is indicated for the same reason as it is in pneumonia and the tank respirator rather than the rocking bed or chest respirator should be used.

The methods used to reexpand the lung will vary in accordance with certain factors. If accumulation or aspiration of secretions have caused collapse of a large segment of one or more lobes, bronchoscopy should be performed as soon as possible, and the occluding substances removed. If possible, this procedure should be carried out under local anesthesia of the pharynx and larynx with the patient in the respirator. When necessary, a general anesthetic should be given. This procedure may be followed by increasing the pressure range of the tank respirator.

of importance in the stage before artificial respiration is employed.

THE COMPLICATIONS OF POLIOMYELITIS AND THEIR TREATMENT

Respiratory Tract Complications.—Infections of the upper respiratory tract, atelectasis, and pneumonia, are the most serious complications which develop in poliomyelitis patients with respiratory deficiency. Fever, which accompanies infection, increases metabolism and heightens respiratory demands Infection of the upper respiratory passages may cause a severe and prolonged reduction of vital capacity and maximum breathing capacity Pneumonia and atelectasis add difficulties by interfering with the absorption of oxygen *from the alveoli into the blood In addition, they decrease* lung compliance, thereby diminishing pulmonary ventilation

1 *Infection of the Upper Respiratory Tract* —Prevention of respiratory tract infection can be aided by keeping persons with obvious or suspected respiratory infections away from poliomyelitis patients During the early phase of respira-

When, despite efforts to prevent it, upper respiratory infection does occur, treatment with large doses of antibiotics should be instituted at once At the same time every effort

of mucus and other secretions from the pharynx by patients with weakness of the muscles of swallowing may cause atelectasis *and pneumonia Atelectasis may also result from* incomplete expansion of the lung due to paralysis of the respiratory muscles or to involvement of the neurones in the medulla which control the breathing mechanisms. Loss of ability to cough is also an important factor in its develop-

ment. When atelectasis is present, dyspnea may be seen and there may be retraction at the sternal notch. Differences in expansion of the chest due to the collapse of portions of the lung may be observed. Dislocation of a palpable apex beat, and auscultation and percussion may reveal the heart to be displaced toward the side of a collapsed lobe or lung Rales and squeaks indicative of fluid in the trachea and bronchi may be heard. Fluoroscopic examination will give a fairly clear picture of the extent of atelectasis The symptoms of anoxia and CO_2 retention may be present Cyanosis, periods of apnea, convulsions, unconsciousness and death may result if relief is not afforded

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When only a small portion of lung tissue is atelectatic, the patient may experience no distress. Bronchoscopy may then safely be postponed and a period of observation with measures designed to promote postural drainage may be tried On the other hand, when the atelectasis is serious, a tracheotomy may be necessary to facilitate repeated deep aspiration of the bronchi Bronchoscopy is sometimes easier through a tracheotomy wound than through the larynx

3. *Pneumonia.*—When pneumonia occurs, intensive antibiotic therapy is instituted at once. Oxygen therapy is definitely indicated Since there is in pneumonia an appreciable flow of blood through unventilated lung, efficient oxygen therapy may increase arterial oxygen saturation. If the patient has been receiving one of the less efficient forms of mechanical therapy, such as by chest respirator or rocking bed, he should generally be transferred to the tank respirator until resolution of pneumonia has taken place

4. *Loss of Lung Elasticity (Compliance).*—Patients with long-standing muscle weakness often suffer a loss of pulmonary elasticity (compliance). The loss of lung compliance is due to many factors among which loss of elastic tissue and replacement by fibrous connective tissue appear to play an important role Patients who have remained in the tank respirator for prolonged periods are especially liable to develop loss of lung elasticity This disability greatly increases the amount of muscular work required to produce a given amount of pulmonary ventilation Because the patients who lose pulmonary compliance are those with the most serious loss of respiratory muscle function, the resulting difficulties may be very serious

Cardiovascular Complications in Poliomyelitis.—These include hypertension, hypotension, shock, myocarditis, and cor pulmonale.

1. *Hypertension* —Hypertension to some degree occurs in about 40 per cent *of all poliomyelitis cases. In most in*stances, the elevation in blood pressure does not persist for more than 7 or 8 days after the onset of illness In a general

way, the severity of the hypertension parallels that of the poliomyelitis infection. Both incidence and severity of hypertension are greater in patients with bulbar poliomyelitis than in those without involvement of the medulla. There is also a similar relationship between the occurrence of respiratory muscle difficulty and the degree and persistence of elevated blood pressure levels. The majority of patients with breathing difficulty and hypertension remain hypertensive for about three months after the onset of illness, and in a small percentage of patients, hypertension persists even longer and may be so severe as to produce encephalopathy with convulsions and cortical blindness. Studies have shown that this persisting hypertension is not due to hypoxia, carbon dioxide retention, or renal disease but results from injury to the neurones which control blood pressure.

2. The *hypertensive crises* and the *hypotensive episodes* and shock which sometimes occur during the acute phase of the bulbar form of poliomyelitis have been described on page 508.

3. *Cardiac Complications.*—Minor degrees of myocardial damage may be clinically undetectable. Often, the first clinical indications of heart injury is a decrease in the volume and a change in the quality of the first heart sound heard at the apex. With increasing myocardial damage, the presence of murmurs, gallop rhythm, and enlargement of the heart may be noted. Finally, obvious signs of cardiac failure such as enlargement of the liver and rales in the lung may appear. Changes in the T-waves and ST segments of the electrocardiogram may be seen in the absence of clinical evidence of cardiac damage. In a number of cases, prolongation of the circulation time has been demonstrated under these conditions.

4. *Cor Pulmonale.*—Disturbance of function of the right ventricle may occur in patients with long-standing respiratory insufficiency as a result of changes in the lungs (cor pulmonale). An increase in pulmonary arterial pressure brought about by lowering oxygen saturation of the blood,

combined with atelectasis and pulmonary fibrosis, increases the work-load required of the right ventricle. Enlargement of this chamber and eventual right-sided cardiac failure and death may result.

Treatment of Cardiovascular Complications.—The abnormalities in blood pressure levels which may occur in the patient with bulbar poliomyelitis may be very serious. Hypertension should be treated when it reaches excessive levels with magnesium sulfate or with Rauwolfia serpentina. Rauwolfia is preferable because of the promptness with which it acts and also because, should hypotension follow its use, norepinephrine will restore the blood pressure to normal levels. On the other hand, magnesium sulfate interferes with the action of norepinephrine should the blood pressure fall to shock-like levels. The veratrum alkaloids should not be used because of the frequency with which they induce vomiting. Hexamethonium is effective but this drug has a tendency to produce adynamic ileus and should therefore be avoided.

Hypotension and shock are treated by such drugs as caffeine sodium benzoate, epinephrine, neosynephrine and norepinephrine. Caffeine sodium benzoate may be given intramuscularly or intravenously as often as every 30 minutes, in doses of 10 mgm. per kilogram or the contents of an 0.5 gram ampoule to an adult. Epinephrine is given subcutaneously or intravenously in a dosage of 0.3 to 1.0 ml. of a 1:1000 solution. Neosynephrine may be given by

epinephrine (Levophed®) is administered in a solution by continuous intravenous infusion. This drug is available in 4 ml. ampoules of a 0.2 per cent solution. The contents of one ampoule are diluted to 1000 ml. with 5 per cent dextrose solution, giving a concentration of norepinephrine of 4 micrograms per ml. After a preliminary test of its effect upon the blood pressure, the injection is continued at a slow

rate varying between 0.1 to 1 ml. per minute, as required to obtain the desired blood pressure response. Unfortunately, none of these drugs appears to be very effective in most cases.

When clinical and laboratory findings reveal only a mild degree of myocardial damage, no particular treatment is required. When evidence of more serious myocardial involvement is present, oxygen administration and digoxin, preferably by parenteral injection, should be employed. The same principles apply to the use of digoxin as those described in the section on diphtheric myocarditis, and the same dosage is employed (see p. 141). The sodium chloride intake of the patient should be kept to a minimum, and water should be restricted to the minimal requirement. However, if evidences of shock are present, restriction of water and electrolytes must be disregarded. A mercurial diuretic should be administered for the same reasons that it is employed for the treatment of myocardial insufficiency of any cause. Mercuhydrin* (meralluride sodium) is given by subcutaneous injection. 0.5 ml. is given as an initial dose for adults and if no reaction occurs, the subsequent injection of 1 to 2 ml. is administered. This dose may be repeated daily as indicated. The dosage for children is proportionally smaller, depending upon the body weight. If the patient is in a tank respirator, the intra-tank negative pressure should be increased. This reduces the venous return to the right side of the heart and decreases the workload required of the myocardium.

Infection of the Urinary Tract.—In patients with bladder paralysis, cystitis and pyelonephritis are common, particularly if catheterization over a long period is required, and it is almost impossible always to prevent such urinary infections. Rather than give antibiotics prophylactically throughout the period of bladder drainage, it may be wiser to make frequent bacteriologic examination of the urine and choose the most effective antibiotic for each infection as it occurs. Infection of the urinary tract favors the formation of calculi

Hypercalcemia and Renal Injury in Poliomyelitis.—The poliomyelitis patient with extensive paralysis is often found to have hypercalcemia and to excrete large quantities of calcium in the urine The hypercalcemia and hypercalcuria are due to atrophy of bone brought about by disuse of the skeleton resulting from paralysis of the muscles of the extremities and the trunk The hypercalcemia imposes upon the kidney the necessity for increased excretion of calcium, the calcuria mentioned being a result of this process. Because of the large quantities of calcium excreted in the urine, formation of calculi may result and in many instances calculus formation is quite extensive It may be so great as to occlude completely the pelvis of the kidney with staghorn calculi, causing secondary renal damage Calcification through the substance of the kidney itself may occur, also with loss of kidney function In addition, hypercalcemia appears to interfere with glomerular function and may lead to damage of this portion of the renal nephron In such instances, there may be an increased excretion not only of calcium but of sodium and chloride with the production of hyponatremia and hypochloremia and the clinical manifestations which these chemical derangements produce

The danger of hypercalcemia and hypercalcuria can be diminished by several methods Plum has stated that forcing fluids to a total of three liters daily (for adults) is an efficient way to prevent renal calcinosis

The atrophy of disuse which occurs in bone as a result of paralysis of the skeletal muscles is due primarily to a loss of the protein matrix upon which calcium salts are deposited When the matrix is lost, the calcium salt enters the blood causing hypercalcemia It is believed by some that testosterone prevents the loss of bone matrix, and consequently it might be expected that it would prevent hypercalcemia and hypercalcuria in poliomyelitis patients with extensive paralysis We have reduced the excretion of calcium, nitrogen, and phosphorus in the urine by 40 per cent by administration of 40 to 80 mgm of testosterone daily. It

has also been stated by some authors that if the patient were kept in upright position by means of a tilt-table, that the loss of calcium from bone and hypercalcemia might be diminished However, accurate observations have shown that this is not the case.

Contractures and Deformities.—Contractures are liable to develop in extremities which have suffered loss of muscle function of considerable degree The same is true of the muscles of the trunk, paralysis of which may lead to severe scoliosis with great deformity As already stated, muscular atrophy is an inevitable sequel to loss of motor function.

THE GENERAL TREATMENT OF POLIOMYELITIS

There are few diseases in the treatment of which so many different specialties are employed Pediatrics and special
n [illegible]
p [illegible]
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ordinated and harmonized by one person, preferably the pediatrician Each case must be individualized, and the patient treated as a whole

The aims of treatment are to save life, to relieve physical and mental discomfort, to minimize after effects, and to rehabilitate the patient Nothing now known can affect the extent of the initial loss of innervation

Care at home is advocated for most patients with only suspected poliomyelitis, nonparalytic cases of the disease, and many of the mild forms even with some little weakness The benefits of such a procedure are definite The patient's welfare is furthered by avoiding the physical and nervous fatigue of the trip to a hospital, hospital facilities needed for more severe cases are not preempted, and the patient's family is saved disruption and expense On the other hand, hospital care is highly desirable or even essential for those cases where there is increasing fever, an appearance of prostration, any urinary difficulty, any suggestion of breath-

ing difficulty, or any signs of possible bulbar involvement such as nasal regurgitation of fluids, or difficulty in swallowing Weakness of a deltoid muscle may foretell diaphragmatic involvement, and is therefore in itself an indication for hospitalization

Specific Treatment.—For poliomyelitis, as for most of the acute virus diseases, we have no specific cure, no drug, chemical, antibiotic, or serum which can be proved in any *way to be curative after the clinical manifestations of the* disease appear All efforts to kill the virus within the host, or by artificial means to neutralize its attack have given only disappointing results Even very large quantities of gamma globulin given in the preparalytic stage have produced no appreciable benefit

General Treatment. — *First Examination* — Particularly when first seen, the patient should be treated in a calm, reassuring and kindly manner not only to lessen his anxiety and nervous tension, but to obtain his full cooperation on which his progress, even his life, may depend. If symptoms suggesting bulbar or respiratory difficulties and possible danger of life are present, the examination of individual muscles is deferred until later so that there may be a minimum of handling Otherwise, the diagnosis should be confirmed and indications for treatment determined including a preliminary study of muscle involvement, particularly as to spasm However, a complete and detailed analysis of muscle weakness, made during the febrile period, is largely valueless because of the simulation of paralysis by inhibition due to spasm, and because of the changing state of muscle innervation during the early days of the illness Furthermore, an exhaustive study at this time is actually contraindicated because of the fatigue and pain it causes the patient.

Individual Isolation —Rigid isolation technic should be established at once, and maintained as long as the local health authorities require, usually either seven or fourteen days. Paper handkerchiefs should be used and burned.

There is no proof that the wearing of masks by doctors and nurses is of sufficient benefit to be made a requirement. It is impossible to prevent most sewage contamination because there can be no control of the healthy unrecognized carriers who are much more numerous than are patients. However, hand contamination from infected bed pans must be avoided by careful hand washing

Bed and Rest.—Dressed only in a loin-cloth and perhaps the top half of pajamas put on backwards, the patient is placed supine in a bed of adequate size with a firm mattress on a bed board, and with a foot board to hold the bed clothing off his lower extremities. He is allowed small pillows under his knees, or his shoulders, or any other place where stretching of a tightened muscle can thereby be relieved, but not under his head because flexing the neck would stretch the long neck muscles which are almost invariably tightened If the patient can tolerate the position comfortably and will cooperate, he is preferably placed with the soles of his feet against a foot board and his extremities in the normal physiological position they would assume if he were erect. However, little children and any others with marked discomfort are usually allowed to lie in any position they will, nature leading them to assume the posture in which they are most comfortable, that is, in which the sore muscles are least stretched

Complete mental and physical rest, quiet, and comfort are sought after, with every effort made to avoid unnecessary procedures and rough handling Treatment that is not definitely indicated is contraindicated Sleep is not interrupted for routine treatments, but on the other hand sleep is not induced by medication for fear of concealing or aggravating respiratory difficulty. Narcotics especially, but also barbiturates, are definitely contraindicated because of their depressing effect on the respiratory center.

Elimination by bladder and bowel is carefully checked. When there is difficulty in voiding. Furmethide®, given subcutaneously in doses of 5 to 7 mgm for an adult, usually

induces urination if it is administered before the bladder becomes markedly distended. In some cases, this drug is not effective, or it may cause untoward side effects (which can be neutralized by hypodermic injection of atropine) If catheterization proves to be necessary and must be repeated frequently, it is usually wiser to install an indwelling catheter

Cathartics are contraindicated especially in the acute stage, serving only to increase intestinal peristalsis and causing cramps, without overcoming the temporary paralysis of the muscles that normally function in defecation. However, an enema may prove more effective if intestinal peristalsis at the time of its administration is stimulated by the subcutaneous injection of 0 25 or 0 5 mg of neostigmine methylsulphate a half hour before The nurse's hand on the patient's abdomen *can usually detect the beginning of the peristalsis* indicating the time for starting the enema

After the acute stage is well past, a saline laxative such as milk of magnesia may prove beneficial without causing distress

Fluid and Nutritional Requirements —During the febrile period of the acute illness, adequate fluids, glucose, and salt should be given orally or parenterally to relieve or prevent dehydration When the patient cannot swallow, hydration is maintained during the next day or two by adequate amounts of a 5 per cent glucose and electrolyte solutions If the patient is perspiring freely, perhaps the result of hot packs or tubs, excessive salt loss should be made up by oral or parenteral administration The body's requirements in vitamins, amino acids, and calories must also receive consideration.

Other Medication.—For falling blood pressure and other indications of shock, stimulants and oxygen may be used. For details of their use see page 508.

For the relief of tightness in muscles, a number of drugs have been recommended such as curare, neostigmine and similar remedies None is probably of sufficient value to be worth using.

For muscle twitchings and actual cramps, quinine in doses of 3 to 5 grains once or twice a day, especially at bedtime, is usually quite effective. The drug acts directly on the skeletal muscle producing a refractory period. Pain is usually relieved and may be completely abolished after one or two doses. Occasionally cramps become less severe or less frequent and eventually cease.

Aspirin may be given freely for the relief of general discomfort. After the acute stage, codeine may also be given when there is no longer danger of respiratory difficulty.

Bulbar cases require special attention and usually expert nursing care on which life may depend. Complete rest and a minimum of handling are essential but these patients are usually very restless and apprehensive and require constant care and consideration. For those patients who cannot swallow, nothing is offered by mouth and the fluid requirements are consequently supplied by vein. The saliva and mucus that accumulate in the mouth must be removed and *postural drainage* and suction are instituted (for details, see p. 498). Skill in their proper use is of the utmost importance for the patient's comfort and welfare. Atropine must not be used because it increases the viscosity of saliva.

After two or three days of feeding by vein, and when the fever is gone, if the patient still cannot swallow his saliva, attempts may be made to pass a plastic feeding tube through a nostril into the stomach unless this procedure tends to cause gagging and vomiting. By tube, a patient may be fed many days until the ability to swallow returns, which is usual in from one to two weeks. During this period of tube feeding, as well as afterwards, special attempts should be made to provide the patient's requirements in calories, proteins, and vitamins. Such proprietary preparations as Sustogen* are of value for this method of feeding.

Gavage feeding should not be started without having the patient's shoulders higher than the stomach. In some patients, the cardia is relaxed and liquids can flow back from the stomach if the head end of the bed is depressed. After

it has become evident that the patient can retain fluids in the stomach, he can be fed when horizontal.

When a patient seems able to swallow his own saliva, very small amounts of water can be offered by teaspoon at half-hour intervals, increasing gradually Milk is not well tolerated the first few days after swallowing returns but fruit juices, sherbets, strained broths, and apple sauce are usually acceptable When the patient is again able to eat somewhat, he should not eat or drink alone, because of the danger of choking as a result of the food or fluid entering a relaxed larynx. If choking does occur, the patient should be placed face down on his bed with the hips elevated, and then patted on the back

Physical Therapy.—The aims of physical therapy in poliomyelitis are to relieve discomfort and pain, to overcome "spasm" or muscle tightness, to maintain muscles in good condition and to prevent or correct deformities, then by re-education to combat muscle incoordination, and to improve muscle control. Later, when control is well obtained, the aim is to increase strength and general body function by exercises which will induce hypertrophy of the muscle fibers which have survived

To facilitate an *evaluation* of the measures used, careful records must be kept of muscle strength and of flexibility by standard scales or measurements Muscle strength is evaluated as follows:

5	N	Normal	Complete range of motion against gravity with full resistance
4	G	Good	Complete range of motion against gravity with some resistance
3	F	Fair	Complete range of motion against gravity
2	P	Poor	Complete range of motion with gravity eliminated
1	T	Trace	Evidence of slight contractility No joint motion
0	O	Zero	No evidence of contractility

It is better to use the figures 0 to 5 than descriptive words because of the possible comprehension of the patient and the resultant effect on his morale, of the use of such words as poor and fair. Periodic recordings of strength tests enable

accurate determination of the progress of the patient's recovery. For recording the results of muscle examinations, The National Foundation for Infantile Paralysis provides an excellent standardized form which has been widely adopted

Muscle tension, or lack of flexibility, is best recorded by the measurement of angles and distances For instance, with the patient supine, the straight leg may be raised at first only 20 degrees, later 40 degrees or 60 degrees The stiffness of the neck, back, and hamstrings may first permit flexion of the spine only to a distance of 28 inches from the forehead hairline to the upper edge of the patella with the hip flexed—but two weeks later this distance may be measured as 10 inches.

For *combating "spasm"* and pain, a number of procedures are available, and their use will depend on the facilities and personnel available, and on the results obtained in each individual case

1 *Hot Packs* —These may be local wrap packs or laid-on packs A doubled piece of wool cloth cut to fit the part is heated by steam or boiling, then wrung essentially dry by passing twice through a wringer, or the cloth may be heated and excess water removed by spinning in a commercially available apparatus designed for this purpose The cloth is then applied as hot as the patient can tolerate Over it is placed a layer of waterproof material and then another layer of wool to hold in the heat These latter two layers may previously have been stitched together Such packs may be pinned and left in place one to two hours, and then renewed every two hours throughout the day, or they may be applied for fifteen minutes just before a session with a physical therapist

With the patient prone, the packs may also be merely laid on from neck to heel, tucked in at the sides of the body and extremities, and changed once after fifteen minutes for two to three such half-hour periods each day.

2 *Hot Baths* —For five to ten minutes, the patient is immersed to the neck in warm water which is then heated

gradually up to 102° F. Cold, such as an ice bag, should be applied to the head, and fluids freely given by mouth Such baths may be given two to three times a day A patient in a hot tub should never be left unattended, because of the danger of fainting

3. *Wet Wraps* —A cotton sheet is wrung out in water at a temperature of about 60° F and wrapped about the patient from neck to toes separating all body surfaces. One blanket in summer and two in winter are wrapped around the patient, who in ten minutes usually begins to perspire. Twice a day *the patient is left in the pack two to three hours and usually*



Fig 80 —Illustrating full flexibility of the spine shown by touching the forehead to the knee in extension The attainment of this position is one of the goals in physical therapy (Courtesy of the National Foundation for Infantile Paralysis)

sleeps most of this period, thereby obtaining both rest and ... These wraps are ... well as for those

For a single tight muscle, such as the gastrocnemius, a local wet wrap left on overnight for a number of nights sometimes seems beneficial

There is a great variation in the number of days or weeks required for obtaining relief of muscle tightness and complete

range of joint motion. With each procedure used, the patient seems to show improvement for possibly three or four weeks, but when his progress seems to "plateau," it might be well to change to a different procedure, the change in itself often seeming beneficial

Physical therapy may begin the first day of hospitalization if the patient's condition warrants, and if his temperature is



FIG 81 —Showing use of dome for artificial respiration during administration of physical therapy

normal The first step is tendon stimulation, which is an attempt on the part of the technician to reestablish reflex action With the patient completely relaxed and paying no attention, a muscle is several times moved passively through a very limited range of motion, and short of causing any discomfort. Stimuli from the nerve endings in the joints, tendons, and muscles, pass along the sensory pathways to the cord and thence back to the muscle by means of the

reflex arc and such motor neurones as may still be alive, are used in an attempt to produce a prominent or "live" tendon This stimulation is done several times a day and with a minimum of disturbance to the patient. Further than this in muscle rehabilitation, the physical therapist usually cannot proceed until all pain has disappeared and until the muscle shortening has been largely overcome, and the muscle has regained its normal resting length. Often actual stretching is necessary to attain this end

The next step is passive motion of a mobile joint performed by the technician but with the patient actively concentrating on the motion. After he thoroughly understands the action desired, he is allowed to move on to the third step of carefully regulated active motion The entire emphasis for many weeks is upon regaining control of a particular muscle or function, rather than upon increasing strength. Balance between opposing muscles is sought, and unsupported weight bearing is not allowed while there is imbalance such as between *the two sides of the spinal column*

For a technician to be qualified and capable to conduct such reeducation of the muscles of a patient with poliomyelitis, careful training is essential The anatomy and function of each muscle must be thoroughly understood, and the proper method of handling each motor problem learned With skillful care, however, amazing results can be obtained in overcoming dysfunction and making the most of markedly weakened muscles In fact, function that is adequate for most purposes can frequently be obtained in muscles that have far from normal strength

The work of the physical therapist can be helped by a skilled *occupational therapist* whose efforts can also be of great value *in improving the patient's morale* A large variety of handicrafts and of forms of art work are available and suitable, but the occupation should be carefully selected according to the patient's intelligence and his physical restrictions and needs So also the coöperation of a wise *psychologist* can be most beneficial particularly with the

older patients and parents But everybody involved in the treatment of a case of poliomyelitis should combine in encouraging the patient to overcome his restrictions and to pass on to achieve a life of usefulness to others, and satisfaction to himself.

When tightness is essentially released and the patient has achieved appreciable control of his major movements, definite efforts should be directed towards *social rehabilitation* and increasing strength A long list of acts necessary for an independent life should be prepared, and the patient trained to accomplish one after another of these functions, such as turning over in bed, moving from bed to a chair, standing, walking, opening a door, feeding himself, brushing his hair or teeth, tieing his tie and the like Substitution of a useful muscle for a weak one is often necessary at this stage For instance, in vary rare cases, where both arms are so weak as to be useless, the patient has to be taught to care for himself with his feet.

Orthopedics.—During the months of reeducation of muscles and of social rehabilitation, orthopedic help is at times essential Posterior moulded splints are occasionally necessary for maintaining desired positions at night When a patient is being mobilized, orthopedic support for weight bearing and against the pull of gravity is sometimes necessary. Then when reeducation has accomplished all it can, reconstructive operations are occasionally needed to stabilize a flail joint, to transplant a live tendon or to correct possible deformities, but such operations ordinarily should be postponed at least until two years from the onset of the illness

THE DIFFERENTIAL DIAGNOSIS OF POLIOMYELITIS

The diagnosis of poliomyelitis can be made with considerable precision by laboratory means By tissue culture techniques, poliovirus can be isolated from the stools and its type determined in the great majority of cases Furthermore, it is possible to demonstrate during convalescence, the

production of type specific polio antibodies in the patient's serum There are a number of research laboratories scattered throughout the country which are capable of making the specific laboratory diagnosis of poliomyelitis, but very few hospitals have laboratories prepared to carry out these routine tissue culture tests for polioviruses. Therefore, since there is no pathognomonic symptom or sign, the diagnosis usually is based on a study of circumstantial evidence such as the findings of a short initial febrile stage, with headache and perhaps vomiting, with muscle tenderness, spasm of the neck, back, hamstrings and occasionally other parts, various vasomotor disturbances, a tremor especially of the hands, somnolence and irritability, irregular reflexes tending to disappear, abnormal spinal fluid findings, and the occasional development of muscle weakness which is customarily *irregular in distribution*

Some other diagnosis should be suggested by continued high fever or any fever over ten days in duration, by local *swelling, or sharply localized pain,* by *loss of sensation,* by entire limitation of passive motion at a particular joint, or by a leukocyte count above 13 or 14 thousand

Differentiation from other diseases depends on the stage or type of the disease In the abortive type of case, it is impossible to diagnose clinically an infection with the virus of poliomyelitis or to differentiate it from the constitutional manifestations of general infections The spinal fluid is entirely normal Nonparalytic or paralytic poliomyelitis in its pre-paralytic stage must be carefully differentiated from a number of other conditions:

1 *Viral Encephalitis* —Several types of viral encephalitis may resemble the pre-paralytic stage of poliomyelitis and examination *of the spinal fluid is of no assistance in the differ*entiation of these diseases because other findings are essentially identical. Encephalitis may be very difficult to differentiate from the bulbar form of poliomyelitis, but encephalitis patients usually present cerebral signs such as stupor and delirium, in contrast to poliomyelitis, in which encephalitic

symptoms are usually much less prominent until the patient is *in extremis* Convulsions are common in encephalitis but very rare in poliomyelitis.

The presence of a rash, or a history of a typical rash, serves to differentiate encephalitis following such diseases as measles and chickenpox from the early phases of poliomyelitis Mumps meningoencephalitis can be differentiated in those cases in which there is swelling of the parotid or a suggestion of tenderness in a testicle In those cases in which no parotid swelling is present, the diagnosis of this disease can be established with a high degree of accuracy by the demonstration of the appearance of complement fixing antibodies against mumps virus (see p 301) In rare cases symptoms of disease of the central nervous system occur in infectious mononucleosis, but this disease can be identified by the presence of abnormal lymphocytes in the blood and by the finding of heterophile antibody in the serum Epidemic encephalitis (von Economo's disease) attacks persons of all ages indiscriminately, is more prevalent in winter than in summer, and in contrast to poliomyelitis, is often followed by symptoms of permanent injury to the brain St Louis, Eastern, and Western equine encephalitis, like poliomyelitis, are summer diseases, being transmitted to man by mosquitoes In these diseases, symptoms of cerebral involvement are striking, and specific complement fixing antibodies develop in the blood during convalescence

2. *Acute Lymphocytic Choriomeningitis* —Infection with the virus of this disease probably causes a generalized illness suggesting influenza much more commonly than it causes its rather characteristic infection of the central nervous system, but the specific diagnosis can ordinarily be made only by demonstrating the development of neutralizing or complement fixing antibodies in the patient's blood.

When the central nervous system is involved by this infection, there are apt to be cerebral manifestations of headache, vomiting, drowsiness, even light coma, also meningeal manifestations of stiff neck and back Ordinarily, there is

only transient if any weakness and there may be temporary sensory changes. The duration of the illness is only seven to fourteen days and recovery is usually complete. The spinal fluid contains up to 2000 cells per cubic centimeter, mostly lymphocytes, and neutralizing and complement-fixing antibodies develop in the serum during convalescence. The virus is present in the spinal fluid as well as in the blood, urine, and nasal discharges. There is no specific *treatment of proven value. The differentiation from mild* non-paralytic poliomyelitis may be impossible without neutralization or complement fixation tests or the tissue-culture isolation of poliovirus from the patient's stool.

The virus of lymphocytic choriomeningitis is pathogenic only to human beings and mice, and is carried usually by mice. Thus, the disease in man is particularly apt to occur in homes that are infested with mice.

3. *Tuberculous Meningitis.*—This infection tends to develop much more slowly than does poliomyelitis, but in exceptional cases the rapidity of its onset may be similar to that of poliomyelitis. The clinical manifestations of the two diseases may be very similar for a time, particularly if the poliomyelitis case is non-paralytic. In the tuberculous infection, stupor is usually more profound, there is apt to be projectile vomiting, and paralysis of the eye muscles is occasionally present. Spinal fluid from cases of tuberculous meningitis contains a decreased concentration of sugar and chloride. Microscopic examination of the fluid usually shows tubercle bacilli, and these organisms can be grown in appropriate culture media and in guinea pigs.

4. *Purulent Meningitis.*—In the early stages of purulent meningitis, whether due to the meningococcus or to other organisms, the onset may be closely similar to those cases of poliomyelitis where spasm of the neck, back, and hamstrings is marked. In poliomyelitis there is ordinarily more pain and muscle tenderness. The knee reflexes may be unequal, but are usually equal in meningitis, where there is also more stiffness of the neck as such, a more definitely positive

Kernig's sign, and more delirium The appearance of a hemorrhagic eruption or herpes suggests meningococcus meningitis. In cases of meningitis untreated with antibiotics direct microscopic examination and culture of the spinal fluid usually reveals the causative organism The spinal fluid sugar concentration is low, in contrast with the normal sugar concentration found in poliomyelitis

5. *Syphilitic Meningitis* —This disease may simulate acute poliomyelitis very closely, both in clinical signs and spinal fluid findings In the former disease the onset is usually more gradual, lasting from a month to six weeks, during which time the patients suffer optic neuritis, have vomiting attacks without nausea, have convulsions, and may show paralysis of the extrinsic ocular nerve A positive specific test of the spinal fluid for syphilis makes the diagnosis clear

6. *Meningismus.—Meningismus is the term usually applied* to a symptom complex due to increase in amount and pressure of an otherwise normal spinal fluid. The condition occurs in the course of other diseases, such as pneumonia, influenza, or the exanthemata, and is evidenced by the usual indications of meningeal irritation, such as headache, vomiting, stiffness of the neck, and a positive Kernig's sign Inasmuch as a normal cell count in the spinal fluid is occasionally found also in poliomyelitis, the differentiation from meningismus may at times be confusing

7. *Serous Meningitis* or *Meningitis Sympathica* —This is a meningeal condition occasionally found when an active infection, such as an otitis media or a purulent sinusitis, occurs near the meninges without actual invasion by the infective organisms Well marked signs of meningitis are present and the spinal fluid shows an increase in amount, in albumin and globulin, and in number of cells, even to several thousand with polymorphonuclear cells predominating The fluid is sterile. The differentiation from nonparalytic poliomyelitis may be difficult.

8 *Coxsackie Virus Infection* —Some of the viruses of the Coxsackie group cause an illness which is clinically indis-

tinguishable from non-paralytic poliomyelitis Coxsackie virus infection only rarely produces muscle weakness, and when it does, the muscle weakness is usually equivocal or slight Coxsackie virus infection can be identified by isolating the virus from the stools and by demonstrating the production of specific antibody in the blood during convalescence. The Coxsackie viruses produce encephalomyelitis and myositis in suckling mice, which makes their isolation and identification relatively easy

9. *Adenoidal-pharyngeal-conjunctival Virus Infection (APC Viruses)* —This group of 17 related viruses are cytopathogenic for cells in tissue culture, but do not cause disease in laboratory animals Three of the types of APC viruses cause disease in man. One type (type 3) causes an illness characterized by fever, sore throat, and conjunctivitis in the majority of cases. In some cases, stiffness of the neck and back and muscle soreness have formed a clinical picture resembling non-paralytic poliomyelitis However, the spinal fluid is normal, and muscle weakness has not been observed in APC infections *APC virus infection can be identified by isolating* the virus from the stool by tissue culture methods, and neutralizing antibodies (type specific) and complement fixing antibodies (group specific) are formed in the serum during recovery.

10 *ECHO, or Orphan Viruses* —At least 13 antigenically distinct viruses, first called orphan viruses, but now called ECHO viruses (enteric, cytopathogenic, human orphan viruses), have been isolated from the stools of human beings. Some ECHO viruses have been isolated from patients suffering from a disease which resembles non-paralytic poliomyelitis, but their true significance as regards the causation of human disease is not yet known. That they can cause human infection, inapparent or otherwise, is indicated by the fact that they are neutralized by human gamma globulin, but they are not *neutralized by types 1, 2 and 3 polio*virus antisera nor by Coxsackie virus antisera, nor are they related to the viruses of herpes simplex. influenza. mumps, or

chicken pox or to the APC viruses ECHO viruses can be grown on monkey and human cells in tissue culture, but they do not affect suckling mice, monkeys or other laboratory animals

The non-paralytic stage of poliomyelitis may also be confused with various general systemic infections, such as typhoid fever, which in unusual cases shows a rapid onset of extreme prostration, high fever, delirium, tremor, and headache. With considerable frequency and often very little excuse, such infections as otitis media, tonsillitis, and even pneumonia, are mistaken for poliomyelitis, particularly in their early stages. The hyperesthesia, fever, and arthritis of *acute rheumatic fever*, and the general body aches of influenza, may also cause mistakes in diagnosis

After paralysis has developed, poliomyelitis must be differentiated from the various other diseases in which muscle weakness occurs The paralysis due to *postdiphtheritic neuritis* is apt to appear at a later period in the course of an acute infection than does that of poliomyelitis, and the preexistence of diphtheria has usually been recognized It must be remembered, however, that in poliomyelitis there may be a very considerable degree of faucial inflammation in the preparalytic stage When the paralysis appears several weeks after an attack of diphtheria, as sometimes happens, the differentiation from poliomyelitis may be very confusing. Diphtheritic paralyses occur at a time when the patient has become afebrile and are usually more gradual in development than are those of poliomyelitis, but may be equally rapid Muscle weakness is usually symmetrical, partial, and not accompanied by spasm In diphtheria the nerve injury almost invariably affects the soft palate, and often the ciliary muscles of accommodation of the eyes These eye muscles are not affected in poliomyelitis Toxic myocarditis also is usually present Furthermore, the spinal fluid is essentially normal and if the patient survives, recovery is complete

Other forms of neuritis, such as those due to arsenic, and lead, and to vitamin B_1 deficiency as in alcoholism, are as a

rule symmetrical They develop slowly, and lack an initial febrile stage. The causative factors are generally easily determined, and the incidence is almost invariably in adults The sudden and afebrile general muscular weakness of *botulism*, progressing to ophthalmoplegia and bulbar paralysis and death from respiratory failure, may also be confused with poliomyelitis. In rare instances, rabies has been mistaken for poliomyelitis

If there is definite sensory change such as of pain, touch, or temperature sense, in conjunction with paralysis, some form of neuronitis, neuromyelitis or encephalomyelitis is indicated, rather than poliomyelitis. The spinal fluid, blood, or filtered nasal washing may show the presence of some virus other than that of poliomyelitis A chemical or cytological examination of the spinal fluid may not help in the differentiation which often can only be made by neutralization tests requiring several weeks The *Guillain-Barré* syndrome is characterized by the gradual development of paresthesias and paralysis but often without appreciable fever or such manifestations as headache, stiff spine, or gastro-intestinal disturbance The deep reflexes disappear but the superficial reflexes may persist The muscles involved in the extremities are usually proximal, rather than distal, and symmetrically weakened on the two sides Cranial nerve weakness is common. However, this disease may exactly simulate poliomyelitis except that the spinal fluid characteristically shows after the first few days a marked increase of protein, lasting several months, but a normal cell count, that is, "albumino-cytologic dissociation" In nonfatal cases of most of these infections, the paralyses and sensory disturbances tend to disappear.

Certain conditions in which there is no true paralysis but rather the appearance of a paralysis may be mistaken for poliomyelitis. In scurvy the extremities may be immobilized by fear of pain, but the reflexes are normal, and there is little fever. Hemorrhage in the gums and the roentgen-ray findings of scurvy may confirm the diagnosis. Hysteria,

especially in young women, and severe chorea may also produce deceptive manifestations, but the reflexes are normal.

Finally, injury to nerves, to bones, and to muscles, must all be considered in the differential diagnosis Fracture of the femur has been mistaken for infantile paralysis, so also subdeltoid bursitis Certain disease conditions, such as tuberculosis of the spine, multiple sclerosis, spinal cord hemorrhages, and transverse myelitis, must also be ruled out

THE PROGNOSIS IN POLIOMYELITIS

From the early manifestations of poliomyelitis it is extremely difficult, if not impossible, to prognosticate the outcome Symptoms of involvement of the central nervous system may be marked and yet no paralysis whatever may ensue In other cases the paralysis may appear within twelve hours of the onset of ill health, and progress rapidly to a fatal termination. The chemistry of the spinal fluid has no definite prognostic value, and a high cell count does not necessarily carry with it a bad prognosis There may be a slightly unfavorable difference in the prognosis if the onset has been sudden, if the temperature continues higher than 102° F., and if prostration is marked and the patient appears unusually ill. Weakness of the muscles of respiration and evidence of bulbar disease are unfavorable signs, since death in poliomyelitis usually occurs as a result of such involvement Hoarseness, and difficulty in speaking or swallowing, and hypertension and irregularities of the pulse are of grave significance because they indicate that the bulbar centers have been injured. The age of the patient is of some importance, the disease being more liable to be fatal, and non-paralytic cases less common during the first year of life and after fifteen years.

For several reasons, statistics as to the results following attacks of poliomyelitis are of limited value. The disease varies greatly from year to year and from case to case. A

given series may or may not include many non-paralytic cases Observers vary greatly in what they observe and a standard method of grading muscle function has only recently *become at all widely used*

Of patients diagnosed in the early preparalytic stage, from 50 to 60 per cent will make prompt and complete recoveries while only 40 to 50 per cent will go on to show evidence of paralysis, the figure varying with the medical profession's care and skill in identifying poliomyelitis in this early stage on the one hand, and in finding even slight evidences of paralysis on the other As long as there is fever, paralysis may develop Furthermore, one cannot be sure there is no paralysis until the patient has been allowed out of bed and has been studied on his feet.

Statistics on the prognosis in poliomyelitis gathered by the National Foundation for Infantile Paralysis show that 50 of every 100 patients diagnosed clinically as having poliomyelitis recover completely (this includes those diagnosed as non-paralytic as well as paralytic). Thirty of the 100 patients have slight muscle weakness which causes no significant handicap. Fourteen per cent of polio patients have muscular weakness and paralysis extensive enough to be a serious handicap, and four to ten per cent die (average of 6 per cent).

Loss of strength in one extremity alone or of one facial nerve alone has a fair chance of complete recovery, but when both upper or both lower extremities are involved there will be permanent weakness in 90 per cent or more of the cases Even without complete recovery of strength, function may be essentially normal or at least efficient. The prognosis as to the future function or usefulness of a particular extremity will depend on which muscles in that extremity are most involved. For instance, an upper extremity with a weakened [illegible] more useful than one with a weakened biceps, [illegible] the triceps. [illegible] ons generally [illegible] al nerve and clear up [illegible]

the nerves supplying the soft palate and pharynx However, an occasional patient continues for years to experience some degree of swallowing dysfunction, and very rarely a large degree of swallowing disability persists Paralysis of the bowel usually disappears quickly, often within a week, and the same is true of loss of bladder function Unfortunately in a few cases bladder paralysis is permanent Poliomyelitis is not followed by change in intellect, but psychologic changes may be quite serious and of long duration.

Death in poliomyelitis is usually due to respiratory difficulties of the kinds described on pages 481 to 504, or to shock due to injury to the bulbar centers which control blood pressure. Sometimes the cause of death can be attributed to myocarditis, or to cor pulmonale Death may occur as early as six hours after onset of illness, but it is more usual for four or five days to elapse before respirations cease Pneumonia or atelectasis is commonly present in cases dying after the first week or ten days Infection of the urinary tract, or renal injury following prolonged hypercalcemia may cause death many months after the acute phase of the disease has passed

PERIOD OF INFECTIVITY OF POLIOMYELITIS

There is no exact knowledge on this subject but patients are probably able to infect others by nasopharyngeal secretions the last two or three days of the incubation period and for the first three to seven days of the fever. The stools may contain the virus from two to eight weeks and it may be that infection from this source is possible throughout this period. Cross infections in hospitals are extraordinarily rare Multiple cases in a family are apt to occur almost simultaneously, suggesting a common exposure.

ISOLATION AND QUARANTINE FOR POLIOMYELITIS

Patients are usually rigidly isolated seven days after the ...toms, or until the temperature has remained

normal forty-eight hours Some states isolate for two weeks. Longer isolation appears of no value. Furthermore, only the paralytic cases or a very small proportion of all the persons infected are ordinarily known to a health department.

Similarly, rigid quarantine for contacts accomplishes little It is impossible to segregate effectively any appreciable fraction of the probable carriers without quarantining the whole community such as a summer camp. In some cities, children known to have been definitely exposed to the disease are excluded from school for fourteen days, but in most states this is not considered essential nor that there is public health necessity for closing a school in case of a school exposure In the 1929 epidemic in Ottawa the schools were kept open, and the incidence of the disease among the children of school age who were kept out of school was proportionately *as great as among those who continued in school* However, when a case of the disease has developed in a child recently in school, it may seem necessary for the psychological effect on the parents to close the class from ten to fourteen days

FACTORS WHICH DETERMINE SUSCEPTIBILITY OR IMMUNITY TO POLIOMYELITIS

Probably the most important factor in determining immunity to poliomyelitis is the presence or absence of antibodies against the virus in the blood For the most part, the immunity appears to be type specific, antibody against type 1 protecting only against type 1 poliovirus. There is, however, evidence that some cross immunity actually exists also, [illegible] When the [illegible] indi- [illegible] nodes associated with the intestinal tract. It probably multiplies in these tissues and perhaps in the "brown fat" and then invades the blood stream Viremia is a common occurrence in poliomyelitic infection in persons without antibody. It is

noteworthy that even in the absence of antibody, the virus does not invade the central nervous system in every case in which viremia occurs In fact, as we have shown above, viremia may be accompanied by no detectable symptoms In many cases, however, symptoms described as "minor illness" above accompany the viremia In perhaps one-fourth of the cases, the viremia is followed by invasion of the central nervous system, and this invasion apparently occurs directly from the blood into the spinal cord or bulb The chance of penetration of the nervous system from the blood stream is dependent upon the invasiveness of different strains of poliovirus. Furthermore, animal experiments indicate that the invasiveness of a given strain of virus can be correlated with the concentration of virus reached in the blood stream, the higher the concentration, the more likely the invasion of the nervous system

Certain other factors seem to be involved in the production of central nervous system invasion These factors include excessive muscular exercise and fatigue, and injury to the mucus membranes of the throat such as occurs in tonsillectomy. Tonsillectomy probably favors the occurrence of paralytic disease in a person who has been infected with the virus, it certainly increases the likelihood of occurrence of the bulbar form of the disease Injections of various substances such as pertussis vaccine and alum-precipitated diphtheria toxoid subcutaneously or intramuscularly also seem to predispose to the occurrence of paralytic poliomyelitis and cause localization of the paralysis in the injected limb in a higher than expected percentage Pregnancy, in the belief of most authors, also favors the occurrence of the paralytic form of the disease, and the mortality rate among women who contract the disease in the third trimester and during the puerperium is higher than it is in non-gravid women of the same age It is also possible that

PROPHYLAXIS OF POLIOMYELITIS

Passive Immunization.—It has been demonstrated that administration before infection, of serum containing specific antibodies protects animals against paralytic poliomyelitis for a short time For example, Bodian showed that if enough antibody was given to chimpanzees to give them a blood poliovirus antibody titer of 1 20 or higher, viremia and paralysis were prevented. These animals, however, did excrete poliovirus in the stools and developed active antibody response

Hammon and his associates attempted to discover whether human beings could be protected during an epidemic of poliomyelitis by the administration of human gamma globulin, which contains antibodies against polioviruses In three epidemics in 1951 and 1952, these workers injected about 27,000 children, ranging in age from 1 to 11 years, with 0.14 ml. of gamma globulin per pound of body weight, and an equal number with a dilute gelatin solution which resembled the antibody preparation in appearance The experience of Hammon and his co-workers in this field experiment led them to the conclusion that during a limited period of time after the injection of gamma globulin, a child exposed to poliomyelitis had a "markedly improved chance of not developing" the paralytic form of the disease The publication of Hammon's report led to the extensive and largely uncontrolled use of gamma globulin during 1953. An analysis of the results obtained by the use of gamma globulin in 1951, 1952 and 1953 led Muench to the conclusion that [illegible] currence [illegible] 1951 and [illegible] exert a protective action during the mass inoculation trials carried out in 1953, and that this reduction was in the order of 50 per cent from the expected number of clinical cases. Muench stated, however, that there was no evidence that gamma globulin modified the severity of cases which occur after its use.

At the present time it is believed that gamma globulin in dosage of 0.14 ml. per kilogram may exert a protective effect if it is given before exposure, and perhaps for one or two days after exposure to poliomyelitis virus Since family contacts of a patient with poliomyelitis have nearly always been exposed for much longer than this period before the original case is discovered, it is believed that gamma globulin in this circumstance is of relatively little value.

For a number of reasons, therefore, the use of gamma globulin should not be considered as a routine public health measure for the prevention of poliomyelitis. However, the results of the field trials with gamma globulin strengthened the belief that effective active immunity might be obtained by the use of safe vaccines and this consideration led to renewed efforts to produce such a vaccine and to use it at the first possible moment in a controlled field experiment

Active Immunization.—In the United States, active immunization of the population against poliomyelitis is needed because virtually no children 3 to 5 years of age have antibody against all three types of poliovirus, and less than 40 per cent of this age group have antibody against even one type In fact, only 50 per cent of persons over 18 years of age have antibody against all three types of virus Furthermore, although there is some evidence that cross immunity may exist among the types, it is probable that antibody against one type of virus does not insure solid protection against the others

Two types of vaccine are used for immunization against virus infections One of these types is the "killed" virus vaccine which induces immunity despite the fact that it contains a virus which has been rendered non-infectious by physical or chemical means, such as ultraviolet light, formaldehyde or phenol The second type is the "live" virus vaccine which contains virus mutants which produce a modified infection only, and yet induces immunity against the original virus disease The modified infection may be accompanied by no clinically recognizable disease (yellow

fever vaccine) or by a recognizable, mild illness (vaccinia) The "killed" type of vaccine has the advantage of producing immunity without producing infection, but its disadvantages include difficulties encountered in "killing" the virus and *problems concerning the establishment of safeguards against* infectiousness "Live" vaccine has the advantage of producing a higher degree of immunity and longer lasting immunity than the "killed" vaccine The disadvantages of "live" virus vaccine include the possible increase in the virulence of the virus mutants and the production of the disease in the injected individual with spread of the infection to other persons.

The only available vaccine for immunization against poliomyelitis is the *Salk vaccine* which is a "killed" virus vaccine in which the virus has been made non-infectious by

minimize the possibility of bacterial infection When the *virus concentration has reached its maximum point, it is* filtered and formaldehyde in a concentration of 1 4000 is added, and the pH is adjusted to 7 0 The virus-formaldehyde mixture is incubated at 37° C until tissue culture tests of this material show that no live virus is present.

It was shown in 1953 that injection of the Salk vaccine into human beings produces antibodies against all three types of polioviruses in persons who had no antibody before the injection, and that vaccination also causes a rise in the antibody titer of those persons possessing antibody before vaccination

During the summer of 1954, the National Foundation for Infantile Paralysis undertook a field experiment to determine whether the Salk vaccine would produce actual immunity as well as antibodies In one portion of this experiment, approximately 200,000 children in the 1st, 2nd and 3rd school grades were vaccinated, and 200,000 of their classmates were given a placebo injection. It is quite clear from the tests

that the vaccine in this field trial was harmless, the number of reactions being relatively very few and no greater in the vaccinated group than in the placebo group. Very careful statistical analysis was carried out by Dr. T Francis, Jr., and his associates at the University of Michigan The results showed clearly that the vaccine had reduced the incidence of paralytic poliomyelitis in the vaccinated group as compared with the placebo control group, while the incidence of non-paralytic poliomyelitis was not changed very much The vaccine reduced the incidence of paralytic poliomyelitis due to type 1 by about 60 per cent, and by 80 to 90 per cent for type 2 and type 3. There were 115 cases of paralytic poliomyelitis due to the three types of poliovirus among the children given the placebo injection, while there were only 33 paralytic cases among the vaccinated children This difference is of a high order of statistical significance The effect on the bulbo-spinal form of the disease was even more striking, 36 such cases occurring in the placebo group and only 2 in the vaccinated group

The success of the 1954 field trial of the Salk vaccine was followed by a large scale effort to immunize as many children as possible before the beginning of the poliomyelitis season of 1955. Accordingly, early in the spring of that year, vaccination of children 6 to 9 years of age was begun with commercially prepared vaccine Early in May, it was discovered that a number of children who had been injected with a vaccine produced by one manufacturer had developed paralytic poliomyelitis within a period after the injection which was within the possible incubation period of the disease. Furthermore, investigation of these cases led to the belief that secondary cases had occurred as a result of contact with these children It is believed at the present time that injection of this brand of vaccine caused 77 primary cases of poliomyelitis of which 61 were paralytic cases There were, in addition, 105 cases of poliomyelitis (80 paralytic) in family contacts of these patients, and 20 cases (17 paralytic)

among community contacts. In all, 202 cases with 11 deaths were attributable to this particular brand of vaccine.

This unfortunate occurrence brought about a cessation of the polio vaccination program and led to the reevaluation of the methods employed in testing the Salk vaccine for the presence of "live" virus before its release for use. It was concluded that more rigid safety testing was necessary and the United States Department of Health, Education and Welfare set up new tests which are now in use, and which have proved to be very effective. These safety regulations require that a large sample of each lot of vaccine manufactured be shown by two tissue culture tests to be free of "live" virus before the vaccine is released for use. The largest manufacturer of polio vaccine has stated that all tissue culture tests of batches of vaccine prepared by them during the nine months following the early summer of 1955 have been negative for "live" virus.

TABLE 15

New York State Polio Cases Reported from May 21, 1955 to October 21, 1955

	Total Number	Paralytic Cases	Rate per 100,000
Unvaccinated	282,000	59	21
Vaccinated in 1954	98,000	4	4
Vaccinated in 1955	351,000	14	4

New York City Polio Cases Reported from June 1, 1955 to November 10, 1955

	Total Number	Paralytic Cases	Rate per 100,000
Vaccinated in 1955 (6 7 years old)	166,000	9	5
Unvaccinated (6 7 years old)	87,000	19	22

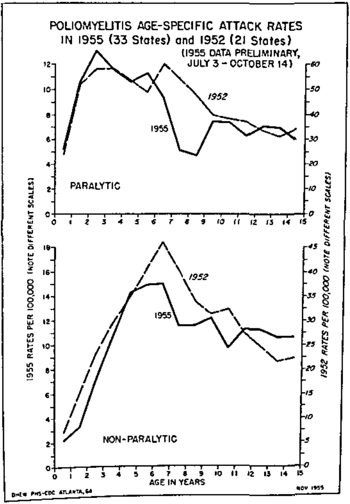
Vaccines which had passed the more rigid safety tests started to become available late in the summer of 1955 and large scale vaccination of children was recommended. As the program progressed and more and more safe vaccine was manufactured, vaccination was extended to include children from 1 to 14 years of age, and in some areas, pregnant women also. By June, 1956, over 40 million children had received

at least one dose of Salk vaccine There is reason to believe that, when properly manufactured and tested, its use is attended by a risk which is extremely small, if indeed it exists at all from a practical standpoint

Evidence obtained during 1955 has made it quite clear that the Salk vaccine is effective in reducing the incidence of paralytic poliomyelitis by 75 to 80 per cent. The vaccine also materially decreases the occurrence of the bulbo-spinal form of the disease The experience of New York City and New York State in 1955 (shown in Table 15) is in general typical of that of the rest of the country It is probable, also, that vaccinated children who did contract the disease suffered a less severe degree of paralysis than did unvaccinated children. It has been estimated that the vaccination program of 1955 in the United States saved some 60 to 70 lives and that it prevented paralysis in 1200 to 1500 children.

A graphic demonstration of the effectiveness of the vaccination program of 1955 is shown in Figure 82 The upper half of the figure shows age specific rates of the incidence of paralytic poliomyelitis for 1952 (when no vaccine was used) and for 1955 The absolute level of the rates for the two years differs, but the two curves have been superimposed by a simple arithmetic transposition The two age distribution curves are similar for all ages except for a sharp decrease in the rates for ages 7 and 8 and in 1955 In other words, 7 and 8 year olds experienced a decreased paralytic poliomyelitis incidence, as compared with 1952, while all other age groups remained unchanged Since the bulk of the vaccination during 1955 was carried out among 7 and 8 year olds, these data furnished independent evidence of the effectiveness of the vaccine against paralytic poliomyelitis

The effect of vaccination upon the incidence of non-paralytic poliomyelitis is much less striking than it is upon the prevention of paralysis This indicates that the vaccine probably does relatively little to prevent poliovirus infection, but that it decreases the danger of virus damage to the central nervous system, and limits the severity of this damage


POLIOMYELITIS AGE-SPECIFIC ATTACK RATES
IN 1955 (33 States) and 1952 (21 States)
(1955 DATA PRELIMINARY,
JULY 3 – OCTOBER 14)
1952
1955
PARALYTIC
1952
1955
NON-PARALYTIC
1955 RATES PER 100,000 (NOTE DIFFERENT SCALES)
1952 RATES PER 100,000 (NOTE DIFFERENT SCALES)
AGE IN YEARS
DHEW PHS-CDC ATLANTA, GA
NOV 1955

At the present time it is recommended that the Salk vaccine be given by intramuscular injection in three doses of 1 ml. each. The second dose is given one month after the first, and the third dose is given at least 7 months after the second injection If necessary, the interval between the first and second doses may be as long as six months without loss of effectiveness Data obtained so far indicate that in most patients polio antibody titer remains at a high level for one year after vaccination, although some unpublished data show that an appreciable percentage of children may not maintain a satisfactory antibody level for even one year It is to be expected that booster injections will have to be given at least every third year

General Measures.—In the presence of poliomyelitis in a community, the public should be advised to take the following precautions·

1 Don't take any drug or chemical aimed to protect against infection There is none that will protect satisfactorily Similarly don't use special nose drops or gargles The mucus on the mucous membranes has protective values

2. Treat any minor illness with immediate bed rest It might be a poliomyelitis infection and easily made worse by "keeping going"

3 Similarly, even healthy individuals should avoid chilling or exhaustion due to fatigue, which may aggravate a possible incubating infection

4 Avoid injury to the nasopharyngeal mucous membranes such as tonsillectomies or tooth extractions It might cause the difference between a symptomless carrier and a severe, even fatal, bulbar case

5 Avoid the use for drinking, swimming, or washing utensils, of any water possibly contaminated by sewage Many apparently healthy people pass the virus in their stools, and sewage has been shown to contain active virus

6 Suppress flies, and in particular protect food from fly contamination Also keep flies away from privies and cesspools Milk for drinking should be pasteurized or boiled

7 Avoid unnecessary personal exposures, such as in movies and other crowded places, also particularly avoid kissing, the use of a common drinking cup and other types of close personal contacts. Avoid traveling to an epidemic area, but fleeing from an epidemic area is usually useless because it will be too late. Children may continue to play with their usual companions.

8. Finally, avoid hysteria and panic. Continue to lead a normal healthy life with special attention to proper, clean food, rest, and moderate exercise. Cleanliness of person and of environment should be enforced constantly

By such measures an individual can perhaps be protected against a dose of the virus large enough to cause the typical disease with paralysis One can hardly hope to escape all exposures, and the child who has been constantly sheltered may be more susceptible than the average when the exposure to poliovirus does occur

A NURSE'S PARTICULAR RESPONSIBILITIES

In the treatment of patients with poliomyelitis, particularly in the acute stage, much depends on the nursing care. Even the survival of the patient may be at stake Many points in which nurses are involved have already been covered in previous paragraphs The following points should particularly be stressed

1 The nurse should constantly have an attitude of calm optimism and cheerful confidence, and never express pessimistic opinions

2. She should handle the patient as little as possible, and avoid tiring him by excessive care. It is far better to allow the acutely ill patient to sleep than to disturb him for a cleansing bath. Don't disturb him with clothes. A loin cloth and perhaps a pajama shirt worn backwards are sufficient clothing for most patients.

3. Grasping tender muscles may increase pain and spasm. If the patient has to be moved, a nurse should handle an

extremity by the joints. Thus, his position should be gently changed several times a day from supine to prone, or from one side to the other. Maintaining proper alignment should be furthered.

4. Care of the skin requires unusual consideration. Pressure points need hardening with rubbing alcohol, especially the necks of respirator patients. Powder on the skin of patients who are perspiring freely from hot packs or tubs, is apt to cake and cause irritation.

5. A bed can occasionally be turned so that the patient will not tend to look or reach to the same side all the time. Another measure to prevent false positions or undue strains is to rest a patient's lumbar area on a pillow when a bed pan is being used.

6. The patient in a respirator needs and deserves constant watchfulness and considerate care. The skin of his neck must be protected from chafing by soft cloths. The position of his body and extremities should be frequently shifted. After the first few days, distractions should be arranged for him, a radio, a television, quiet cheerful visitors, reading aloud, a mirror for indirect vision out a window or door.

7. The nurse must constantly watch how much the patient is eating, not only to insure an adequate intake of calories, vitamins, fluids, and amino acids, but also to guard against overweight as well as underweight.

8. Above all, a nurse should strive for team work with all those working for the patient's welfare, the doctors, the physical therapist, the occupational therapist, perhaps the school teacher, and the other nurses. Team work is even more important than individual skill.

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16

General Management of Contagious Diseases

In the general management of a contagious disease, whether in the hospital or home, three definite objects must be held constantly in mind, (1) giving adequate care to the patient, improving his comfort and well-being, and producing the earliest possible cure; (2) preventing the spread of the disease to others; (3) preventing the patient's being attacked by some secondary infection with resulting complications

The solution of these problems is founded on certain definite principles Of these, the first is that contagious diseases are commonly spread from one patient to another by contact Contact may be direct, as when one touches a person suffering from a contagious disease or is coughed or sneezed upon by a patient, or contact may be indirect as when one touches an object which has been touched either by the patient or by something else that the patient has touched For instance, a nurse who has touched the toys on the bed of a chickenpox patient, and then carries dishes to a measles patient without first changing her gown and washing her hands may easily carry the chickenpox infection with the dishes.

The second principle is that to prevent the spread of contagion, contact of any type must be prevented in every possible way, and where prevention is not possible, contact must be immediately counteracted by concurrent disinfection A nurse is inevitably in contact with a patient when she gives him a treatment or a bath, her resulting contamina- must be immediately counteracted by washing her hands

with soap and water and changing her gown before she may have contact with another patient.

To a certain extent at least, one must also recognize that some contagious diseases may be air-borne. Besides the spread by cough droplets which may extend five feet, moist dust particles can certainly spread streptococci, and dust particles or drops of moisture enable chickenpox, smallpox and possibly pertussis to be carried an indefinite distance, particularly if there is a draft or a breeze. For this reason any action which increases the content of infected particulate matter in the air should be avoided. Shaking of blankets and dry sweeping of floors should not be permitted, and measures which reduce dust formation, such as wet mopping and oiling of blankets, should be used. Because drafts permit great distribution of infectious agents carried in dust particles, they should be guarded against by keeping doors and windows closed whenever this is practicable.

The final principle is that in the presence of contagion, secondary infections, particularly of the upper respiratory tract, are usually as contagious as is the primary disease For example, a measles patient who is suffering also from bronchopneumonia should be as rigidly isolated from another measles patient as if the secondary disease were scarlet fever rather than bronchopneumonia

Some patients are *hyper contagious* such as those with nose or ear discharges, or with purulent skin infections, or early "taking" vaccinations, or those with smallpox or chickenpox. Some are *hyper susceptible*, such as premature infants or patients with infantile eczema, or extensive burns, or poliomyelitis patients with respiratory difficulty.

In addition to an understanding of these problems and principles, a knowledge of the answers to the following questions is essential for the intelligent management of the individual contagious diseases.

1. *Exposure.*—What constitutes exposure to a given disease? At what stage in a disease is it communicable and what secretions harbor the contagion? May a patient remain a carrier and by what means may a carrier be detected?

2. *Immunity.*—How can the presence of immunity be determined and if absent how can it be obtained?

3. *Incubation.*—After a known exposure, how long a time elapses before the onset of symptoms? What supervision is necessary?

4. *Onset.*—On what evidence can the presence of a disease be first suspected and isolation established? On what facts may the diagnosis be based?

5 *Complications*—What complications might occur and what can be done to prevent them?

6 *Treatment*—What can be done to cure these diseases, to clear up carriers, and in general to render the patients no longer contagious?

7. *Communicability*—How do the diseases compare in transmissibility and in difficulty of isolation?

8. *Regulations*—What are the isolation and quarantine regulations of the local health authorities?

The answers to these questions are for the most part covered in this book in the discussions of the particular illnesses, and only those who are well versed in these details can hope to cope successfully with the problems of management of the contagious diseases

In any situation, whether it be in hospital, infirmary, or home, and likewise in the case of almost any of these contagious diseases, there are certain features of the management of individual cases besides the isolation of the patient, which should be stressed.

1. Rest in bed is essential, at least for the duration of the fever and from one to three days longer, depending on the severity of the disease and the resulting weakness of the patient. An added advantage of keeping contagious patients in bed is that maintenance of isolation is thereby facilitated.

2 An abundance of sunshine is important. Viruses and most bacteria are killed by sunshine and drying Fresh air is also essential for the patient's well-being, but where the respiratory mucous membranes are inflamed, the air should be at least 70° F. in warmth. Cold air passing

over the upper respiratory mucous membranes is automatically warmed before it reaches the lungs, and where the cold is excessive an extra blood supply or congestion of the membranes ensues. If the congestion is already marked, due to an infection, the trouble is aggravated. On the other hand steam inhalations of warm moist air are both beneficial and relieving, not only to laryngitis but also to severe head colds and any other upper respiratory infection In fact in such cases, warmth of the air is even more important than its freshness. The patient as a whole, as well as his mucous membranes, should be well guarded against chilling.

3. Plenty of fluid should be given in order to dilute the poisons produced in the patient's body by the infection, and to wash them away *via* the kidneys Fluids, particularly water, should be offered to the patient frequently without waiting for the patient to ask for them When the patient is unable to take much fluid by mouth, it is frequently desirable and necessary to give fluid by some other route such as under the skin, or especially by vein

4. Proper elimination both by the kidneys and by the bowels should be carefully watched and attended to. In certain of these diseases, such as meningitis and poliomyelitis, the bladder may not function properly, and serious distention may occur unless prevented The bowels should move at least every other day, and there are cases where a daily enema is beneficial. Drastic purges are not desirable

5. Treatment for fever as such is not usually necessary In many of the diseases the hyperpyrexia does not last very long, and on the other hand, the depressing effects of such drugs as the coal-tar antipyretics may be undesirable

6. Rest is of very great importance and insomnia should be combated. As far as possible, treatments, medications, meals, etc., should be arranged to coincide, so that between times the patient may have long periods of undisturbed quiet and rest. Too much handling and fussing over a patient is usually distinctly harmful.

7. For most of these diseases no particular diet is indicated. While a patient in bed does not require much fuel to keep up his activity, fever, on the other hand, causes much wasting unless the body nutrition is maintained, hence the caloric intake should be carefully watched During convalescence it is usually advantageous to find out what foods the patient would like and to allow them, albeit in very small quantities if difficult to digest

8. The cleanliness of the patient should receive unusual attention Rubbing the skin with alcohol is very desirable both for the care of the skin and for the patient's comfort, except where the skin is inflamed, as in scarlet fever, when the application of alcohol may be disturbing The sicker patients should be particularly protected against bedsores The mucous membranes of the eyes, nose, and mouth should receive especial care, so that by means of cleanliness the possibility of a secondary infection will be minimized The occurrence of skin infections complicating the skin lesions of chickenpox and smallpox should be combatted by daily cleansing baths

9. Protection against secondary infections, not only with other contagious diseases, but particularly with upper respiratory infections, should be zealously promoted Attendants with an upper respiratory infection, even though it be merely a mild cold, should be kept away from a patient with a contagious disease, for the bacteria which may cause a mild illness in one person may cause a fatal complication, such as bronchopneumonia, in a patient with a contagious disease In general, the prophylactic use of antibiotics is, of course, of value in preventing secondary infections

In general wards for children the preventive administration of an immune globulin or serum to each child on admission may protect those children for the next two or three weeks from ward epidemics of some of the common contagious diseases, though not from upper respiratory infections

Finally, cooperation with the health officers of the community should be furthered to the utmost. Prompt notifi-

cation should be made of the existence of the contagious disease, and the local regulations of the health authorities should be assiduously followed The greatest good for the greatest number demands this cooperation; fair play requires it. People are apt to be annoyed when neighbors do not live up to the requirements of the health authorities, but when the disease is in their own homes they are frequently eager to have an exception made in the control of the case.

The management of contagion is subject to some variation depending on the circumstances, whether it be in a hospital, some such institution as a boarding school, a day school, or a home.

MANAGEMENT OF CONTAGIOUS DISEASES IN HOSPITALS—MEDICAL ASEPTIC TECHNIC

Under present conditions, the great majority of patients ill with most of the common contagious diseases should be treated at home. This applies particularly to measles, chickenpox, and whooping cough, in which a secondary infection may be more serious than the original disease, and is more likely to occur in the hospital than in the home However, when complications have occurred, or when proper medical care of an uncomplicated case can not be provided at home, hospitalization may be necessary.

The proper management of cases of contagious diseases in hospitals is accomplished by means of an exact technic called "Medical Aseptic Technic." This technic was started by Grancher in Paris about 1889 and has since been developed by many workers to its present perfection, the details varying somewhat in different hospitals. It is founded [illegible] to [illegible] ure [illegible] an obvious focus of contagion, such as a patient or his secretions, such contact resulting in so-called contamination of the

object or persons doing the touching Indirect contact is the touching of some object that has been thus contaminated. The technic assumes that infection is not spread through the air, except under conditions of close proximity, as when a patient coughs or sneezes directly in another's face, and the spray from coughing or sneezing is considered effective as a contaminating force over a distance of only about 5 feet from the source Medical aseptic technic involves, therefore, the complete *isolation* of the patient and all objects within 5 feet of his head, the prevention of unnecessary contacts between the patient and other people, and where contact does occur, its immediate counteraction by so-called concurrent disinfection.

This medical technic is comparable to operating room technic, and can be readily adapted to a given situation by any one conversant in the latter. When an operating room is "set up" for an operation, an outsider may enter the room, and provided he touches nothing before he leaves, does no damage; but should he touch a sterilized object, that object becomes contaminated, and must be sterilized. Similarly an outsider may enter the contaminated vicinity of a contagious patient, if he leaves without touching anything, no damage is done; but if he touches a contaminated object, the part which touches that contaminated object becomes contaminated itself and must be disinfected Thus medical aseptic technic is the exact opposite of surgical aseptic technic, in the latter, the object touched must be resterilized; in the former, the touching object must be disinfected

There are three degrees and types of medical cleanliness (1) "Contaminated," wherein the object has been directly or indirectly in contact with a patient and thus has become the conveyor of an infectious virus or microorganism capable of causing a contagious disease, (2) "sterilized," in which all microorganisms are known to have been killed; and (3) "clean," wherein an object, while not necessarily sterile, is at least free from contamination with an infectious agent Thus surgical technic differentiates between sterilized objects and

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MANAGEMENT OF CONTAGIOUS DISEASES IN HOSPITALS—MEDICAL ASEPTIC TECHNIC

Under present conditions, the great majority of patients ill with most of the common contagious diseases should be treated at home This applies particularly to measles, chickenpox, and whooping cough, in which a secondary infection may be more serious than the original disease, and is more likely to occur in the hospital than in the home. However, when complications have occurred, or when proper medical care of an uncomplicated case can not be provided at home, hospitalization may be necessary

The proper management of cases of contagious diseases in hospitals is accomplished by means of an exact technic called "Medical Aseptic Technic" This technic was started by Grancher in Paris about 1889 and has since been developed by many workers to its present perfection, the details varying somewhat in different hospitals. It is founded on the principle that contagion is spread from one person to another by contact only, either direct or indirect. The nature of direct contact is self-evident. It consists of touching an obvious focus of contagion, such as a patient or his secretions, such contact resulting in so-called contamination of the

the non-sterilized, whether the latter be frankly contaminated or just clean. Medical aseptic technic differentiates between contaminated objects and non-contaminated or so-called "clean" objects, which might incidentally be sterile also

In planning the medical technic around a given patient, the zone of contamination, called the unit, is sharply defined and made as closely restricted as possible. It may consist of a room with or without an adjacent bathroom, or of the

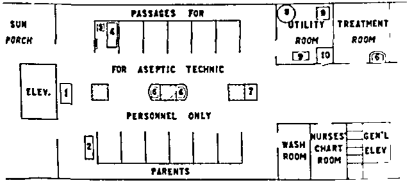


Fig. 84 —A cubicle ward, showing elevator for incoming patients Instru- [illegible]

cubicles

space enclosed by partitions in a ward to comprise a cubicle or finally in an open ward, of an area of invisible boundary, containing the patient and his bed, a bedside table with the patient's articles (such as reading matter or toys, tooth-brush, thermometer, comb and brush, washbasin, soap, face [illegible] Where [illegible] distance

Under most circumstances a unit should contain only one patient, but when two or more patients are known to have the same disease and to be free from secondary infections,

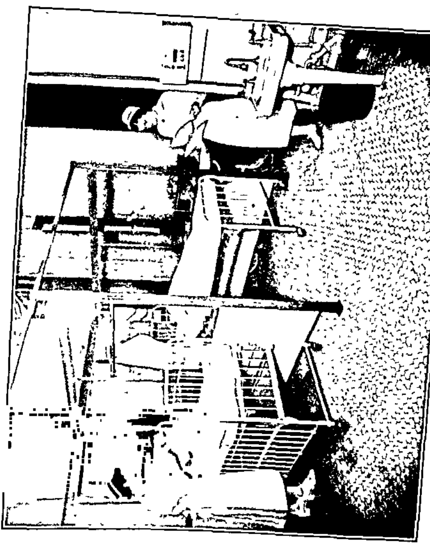


FIG 83 — Demonstration cubicles, the former Willard Parker Hospital Note some of the items mentioned in diagram on opposite page

admit them as such or not, because individuals already under care for other reasons often develop a communicable disease to which they were exposed before or after admission. Moreover every hospital unwittingly admits individuals who are carriers of respiratory or enteric pathogens, or who have open undiagnosed tuberculosis Measures necessary for the prevention of cross infection in hospitals are with few exceptions adequate for the proper care of known communicable disease admissions Definition of the essential elements in hospital procedure and technique is dependent upon the potential routes of spread of infectious agents. All known communicable entries can be fitted into one of four groups Upper respiratory as illustrated by pneumonia, diphtheria and measles, gastrointestinal as with typhoid fever and the dysenteries, membranous and dermal as with venereal diseases and impetigo; and parenteral as with serum hepatitis and malaria Control of these avenues by which infection may spread entails sound planning of all aspects of hospital operation including the dietary department, laundry, housekeeping, sewage disposal, personnel management, and direct patient care Upon such a foundation special techniques are supported without disruption of basic hospital procedure Only when adequate medical aseptic technic is practiced on all services at all times it is possible to block effectively the spread of disease from one patient to another, from patient to attending personnel, or the reverse Interesting studies with ultraviolet irradiation, germicidal mists, etc, offer promise for the future, but for the present cannot be relied upon for the control of cross infection.

articles will be contaminated only while in use and, after being properly disinfected, can be returned to a clean area Each member of the staff should be instructed as to the status of the various areas and objects in use

they may be assembled in the same unit, thereby simplifying nursing and medical care. Thus a whole ward, or several beds in a ward, may comprise a unit.

Details of the technic must vary somewhat with conditions presented by the individual hospital. The indispensable requirements are complete isolation of the patient, prompt *disinfection of every article which comes in contact with* him, and convenient facilities for the thorough surgical cleansing with soap and running water, of the hands of every attendant. The patient must be prevented from transferring infectious material to another individual and the latter must be prevented from bringing further infection to the patient. A complete understanding of and compliance with the details of the technic are indispensable for everybody who enters the unit or deals in any way with the patient and his belongings. The inability of a patient to move from his bed or room, or else his complete loyalty in following out the regulations, is also essential The method permits the care of most contagious diseases side by side in the same ward, without the occurrence of cross infections, and with a reduction in the number of complications Smallpox is so highly contagious that it is an exception and should be cared for in a separate building. It is also extremely difficult to maintain the technic at such a high standard that measles and chickenpox are not carried from one patient to another, so these diseases as well should be segregated on a separate floor or in separate rooms.

DETAILS OF PATIENT CARE[1]

General Principles —In the interest of efficiency in the use of physical space and professional personnel a majority of hospitals admitting communicable disease patients must care for them in the same general area as non-infectious patients Actually all hospitals handle such patients whether they

[1] The material under "Details of Patient Care" is from a pamphlet entitled "Admission to General Hospitals" published in 1955 by the American Academy of Pediatrics, and reproduced by special permission

Management of Diseases Transmissible through Respiratory Secretions.—This group includes diphtheria, streptococcal infections, smallpox, rubeola, rubella, mumps, pertussis, all forms of meningitis, poliomyelitis, the common cold, influenzæ, pneumonia, tuberculosis, and possibly infectious hepatitis Such patients are best cared for in private rooms, but if it is necessary, they may be grouped by diseases in wards Even then it is preferable that they be *in separate permanently walled cubicles.*

Personnel should wash whenever their hands have been contaminated whether by direct contact with the patient or indirectly by contact with possibly contaminated objects A gown should be worn whenever there is actual contact with the patient

It is also recommended that personnel wear masks[1] at all times when in the vicinity of patients with respiratory diseases It is realized that opinion regarding the value of this procedure varies widely. However, until conclusive proof indicating the complete futility of masks is at hand, any error in advising their use is on the side of safety

Concurrent disinfection involves specifically the proper disposal of oral and nasal discharges as will be described in a subsequent section (page 566) Feces disposal by special methods is of importance only in the case of poliomyelitis and infectious hepatitis,

Discharge.—This type includes typhoid, and all other illnesses due to the various Salmonella organisms, bacillary and amebic dysentery, infectious hepatitis, and possibly poliomyelitis

Personnel should wear a gown whenever in contact with the patient and should wash hands whenever they become contaminated directly or indirectly. The use of masks is defensible during the

worn longer than an hour in a contagious disease hospital

In general, contaminated areas include

- Floors
- Patients' rooms or units, and all contents
- Inside of sinks and hoppers

Clean areas include

- Halls
- Nurses' stations
- Cupboards for linen, medicine, and other supplies
- Kitchens
- Utility rooms, except for obviously contaminated sinks or containers

Although it is not economical for the general hospital to hold space vacant for the potential admission or transfer of patients with communicable disease, it is usually possible to designate, in advance, private rooms which are well situated and equipped for the purpose and which can be available in time of actual need When consideration is being given to which rooms might be selected, it should be remembered that running water is essential In the event that individual rooms are not available, admission of patients with the following diseases to open wards or semi-private rooms is acceptable provided that permanent floor to ceiling cubicles are provided

- Chancroid
- Common cold
- Conjunctivitis, acute, infectious of the newborn
- Dysentery, bacillary or amebic
- Glanders
- Gonorrhea
- Impetigo contagiosum
- Leprosy
- Lymphogranuloma venereum
- Meningitis (all forms)
- Pneumonia
- Poliomyelitis
- Ringworm
- Salmonellosis
- Scabies.
- Streptococcal infections
- Syphilis (infectious)
- Tuberculosis (pulmonary).
- Tularemia.
- Typhoid fever.

The first category, namely, insect-born disease, does not constitute a real problem from the standpoint of communicable disease control In the first place the presence of virus in the blood in most instances precedes the onset of clinical symptoms Secondly an extrinsic incubation period in the appropriate insect vector roughly seven to fourteen days is usually necessary before the disease can be transmitted to a human Finally as an essential part of environmental sanitation in any hospital, sufficient attention must be paid to adequate screening and insect control

A fundamental consideration in care of all hospitalized patients is proper sterilization of all equipment in any type of intravenous or other parenteral injection or removal of blood from the body Failure in this connection has been shown repeatedly to have resulted in cross infections with homologous serum and infectious hepatitis As a part of transfusion technique routine serological tests for syphilis are performed, and examined with special reference to primary and secondary syphilitic lesions Routine hematologic examinations of prospective donors for evidence of dormant malaria are of no practical value, but a past history of malaria should always be sought

BASIC PROCEDURES

[illegible]

to any patient Insofar as it is possible, the need for procedures should be explained to the patient, to encourage his co-operation, and help him accept what appears to be rejection

Hand Washing

Sinks with foot or knee controls and a constant supply of hot and cold water, mild soap or detergent, and absorbent paper towels are essential equipment for the establishment of adequate hand washing technics An individual room which does not contain a sink should have easy access to one in an adjoining bathroom If the water supply is controlled by hand faucets instead of the more desirable foot or knee levers, it is suggested that the faucets be washed off when the hands are first lathered This will eliminate the use of paper squares, a procedure which has never been en-

Concurrent disinfection is dependent upon available sewage disposal facilities. Excreta from patients in this category should be handled in accordance with the technique described in a subsequent section (page 566).

Complete and adequate screening should be required in every hospital. It merits special emphasis, however, in any recommendations regarding the care of enteric diseases because of the role of the house fly as a mechanical vector of these infections. Spraying with D D T or similar insect repellents will serve to reinforce other fly control measures.

Management of Diseases Transmissible by Contact with Skin and Mucous Membranes.—This group includes impetigo, scabies, actinomycosis, syphilis, gonorrhea, staphylococcic infections, the gas gangrene group of organisms, and tetanus. Smallpox and streptococcal wound infections may also be spread by the skin and mucous membranes.

Personnel should follow the technique described in the preceding section "Management of Diseases Transmissible through Gastrointestinal Discharges."

Concurrent disinfection for these diseases varies widely in detail. In the case of smallpox, which is highly communicable through the respiratory route, and in which the virus is present in material from skin lesions as well, the most rigid precautions are indicated as advised in the section "Management of Diseases Transmissible through Respiratory Secretions." At the other extreme are cases of tetanus without open wounds. Such patients need be isolated only because of their extreme irritability and so as to avoid unnecessary noises. Syphilitic patients are rendered non-infectious so rapidly by penicillin, that few hospitals maintain any isolation precautions after the first twenty-four hours of treatment, but during that period rubber gloves are advisable. The management of all other diseases in this group is based on the presence of the infective agent. Contaminated dressings and other expendable materials should be placed in paper bags and incinerated. The care of permanent equipment, such as linens and utensils, is described in subsequent sections. Where there has been contamination by spore-forming organisms, autoclaving is the only reliable method of sterilization.

Management of Diseases Transmissible by the Parenteral Route.—This group includes diseases spread by insect vectors, syphilis and malaria when acquired by transfusion, and infectious and serum hepatitis when the infection is the result of transfusion or poor syringe technique.

instances precedes the onset of clinical symptoms Secondly an extrinsic incubation period in the appropriate insect vector roughly seven to fourteen days is usually necessary before the disease can be transmitted to a human Finally as an essential part of environmental sanitation in any hospital, sufficient attention must be paid to adequate screening and insect control

A fundamental consideration in care of all hospitalized patients is proper sterilization of all equipment in any type of intravenous or other parenteral injection or removal of blood from the body Failure in this connection has been shown repeatedly to have resulted in cross infections with homologous serum and infectious hepatitis. As a part of transfusion technique routine serological tests for syphilis are performed, and examined with special reference to primary and secondary syphilitic lesions Routine hematologic examinations of prospective donors for evidence of dormant malaria are of no practical value, but a past history of malaria should always be sought

BASIC PROCEDURES

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Hand Washing

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Extensive studies on the efficacy of some of the newer detergents, particularly those containing hexachlorophene, in hand washing

indicate that these substances are more efficient and more rapid in action than are the usual neutral soaps. They are, however, most effective in solution and this necessitates some sort of dispenser. If soap is used, the cake form is preferable Liquid soap dispensers, if hand operated, are hard to keep clean and even if they are foot-controlled, the solution tends to clog the outlet

The use of a brush is not advised. The procedure outlined below should be followed whether a mild cake soap or one of the newer detergents is employed Specific directions as to the amount of detergent solution to be used are supplied by the various manufacturers

Procedure —Time required—approximately 90 seconds.

1 Standing well away from the sink, turn on water to temperature comfortable to hands

2 Moisten hands and apply a heavy lather of soap, covering well beyond the area contaminated Pay particular attention to the areas between the fingers and under the nails

3 Rinse thoroughly under running water, allowing water to flow from above toward the finger tips.

4 Repeat steps 2 through 3.

5. Dry hands thoroughly

Gown Technic

In the interest of safety and simplicity, it is strongly urged that the "discard method" be employed in the use of gowns With a clean gown each time, there is no danger of contamination from previous use and it is difficult, if not impossible, to insure this when gowns are used for varying lengths of time and by several workers.

Discard Technic.—To Don Gown —Since the gown will be clean each time, it is necessary only to be sure that the uniform is well covered and tapes or hooks securely fastened

To Discard Gown —1. Untie waist tapes.

2 Slip out of gown rolling clean side out over hands and forearms as it falls forward.

3. Discard in laundry hamper

4. Wash hands

If the "Discard Method" is presently not feasible, the following technic should be employed until such time as facilities are adequate for the simpler procedure

To Remove Gown for Future Use —1. Untie waist tapes and drop to side.

2. Push sleeves up far enough to permit handwashing without wetting cuffs.

3 Wash hands

4. Unfasten neckband and slip out of gown without touching the outside

[illegible]

To Don Gown Which Has Been Worn.—1 With clean hands, palms together, open gown at neck. Being careful to touch only the inside of the garment, remove it from the hook.

2 Slip one arm at a time into the sleeves, and from the inside pull the gown well up over each shoulder

3 With hand still clean, fasten the neckband.

4 Bring the two edges of the gown together in back, with clean sides touching, and make a roll of the excess material until it fits the body closely This prevents contamination of the gown through overlapping. Tie waist tapes snugly.

Mask Technic

Gauze (cheese cloth), 42 × 42 threads per square inch, is the preferred material for masks They may be made with four strings and some pliable material to insure fit over the nose, or made on the bias with only two strings. To be effective, masks should always be worn in such a manner that mouth and nose are well covered. They should be changed frequently and never worn after they have become wet They should be disposed of immediately after use and never worn hanging around the neck nor be carried in pockets. Since infectious material which is droplet-borne can contaminate exposed conjunctivæ of attendants and from there pass readily through the conjunctival sac into the nasopharynx, some recommend glasses as well as masks. Masks should be handled as indicated below.

To Don Mask —Unfold mask and place over mouth and nose If there are two sets of strings, it is often more comfortable to place the lower strings around the ears first, and then tie them under the chin The upper strings should be tied firmly at the back of the head If the mask has only one set of strings, these should be tied firmly on top of the head

To Remove Mask.—1 Wash hands.

2 Untie strings and hold mask by strings only

3 Place in labelled container for used masks

indicate that these substances are more efficient and more rapid in action than are the usual neutral soaps. They are, however, most effective in solution and this necessitates some sort of dispenser. If soap is used, the cake form is preferable. Liquid soap dispensers, if hand operated, are hard to keep clean and even if they are foot-controlled, the solution tends to clog the outlet.

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Procedure —Time required—approximately 90 seconds

1 Standing well away from the sink, turn on water to temperature comfortable to hands.

2 Moisten hands and apply a heavy lather of soap, covering well beyond the area contaminated Pay particular attention to the areas between the fingers and under the nails

3 Rinse thoroughly under running water, allowing water to flow from above toward the finger tips

4 Repeat steps 2 through 3

5 Dry hands thoroughly.

Gown Technic

In the interest of safety and simplicity, it is strongly urged that the "discard method" be employed in the use of gowns With a clean gown each time, there is no danger of contamination from previous use and it is difficult, if not impossible, to insure this when gowns are used for varying lengths of time and by several workers

Discard Technic —To Don Gown.—Since the gown will be clean each time, it is necessary only to be sure that the uniform is well covered and tapes or hooks securely fastened.

To Discard Gown —1 Untie waist tapes.

2 Slip out of gown rolling clean side out over hands and forearms as it falls forward.

3. Discard in laundry hamper.

4 Wash hands

If the "Discard Method" is presently not feasible, the following technic should be employed until such time as facilities are adequate for the simpler procedure

To Remove Gown for Future Use.—1. Untie waist tapes and drop to side.

2 Push sleeves up far enough to permit handwashing without wetting cuffs

she should carry out gown and handwashing technics as for other care

Collecting Dishes and Trays.—It is good practice to sterilize all dishes from all patients. Although it is not necessary to have a special kitchen for dishes and trays from patients with communicable diseases, an area should be designated, in the regular kitchen, where trays and dishes from communicable disease patients can be prepared for sterilization. Wax paper bags or thick newspapers should be provided to receive solid food wastes and a pitcher or jar for liquid wastes.

Both solid and liquid food waste should be taken from the kitchen to the utility room and disposed of there, the solid waste in the refuse container and the liquid waste in the hopper or toilet. In situations where special treatment is indicated for stools and urine, liquid and solid food wastes should be disposed of in the same manner.

Dishes and trays should be placed directly in the dishwasher-sterilizer, if one is available or on the stove to boil for five minutes in a covered kettle. If it is not feasible to boil the trays, they may be thoroughly washed, rinsed in actively boiling water, and left to dry. Clean dishes and trays may be stored in the clean area of the kitchen. *The use of paper plates, cups, tray cloths and napkins* is becoming increasingly popular in communicable disease nursing, and the expense is compensated for in the economy of time and effort expended. Paper salt and pepper shakers, which are now available, eliminate another problem in isolation technic

Care of Linen

The laundrying process in a modern hospital should be sufficiently thorough to render soiled linen free of pathogenic material in all but exceptional instances. In spite of the fact that all laundry receives the same treatment, it is common practice to process contaminated linen after so-called "clean" laundry has been finished. Under these circumstances special bags for contaminated linen are provided. Laundry chutes may be used with safety if bags are tightly closed

Linen from individual patients may be collected in the discarded

posal in the special bag, taking care not to touch her uniform or anything else en route. She should, of course, wash her hands after this procedure

Disposal of Wastes

Body Discharges - Nasopharyngeal Discharges and Sputum.—Paper tissues and paper bags for the disposal of nasal secretions should be provided at every bedside and every patient should be instructed concerning their proper use Patients should be taught to expectorate into disposable sputum cups to which a layer of sawdust has been added as absorptive material to avoid spilling Both the paper bags containing the soiled tissues and the sputum boxes should be collected at frequent intervals At the time of collection, the paper bags should be added to the sputum box and the box wrapped securely in paper Both should be discarded in a special refuse container in the utility room for final disposition by burning

Stools and Urine.—In general, bedpans may be emptied directly into the hopper or toilet, paper towels being used to operate both the flusher and the sterilizer

In the case of typhoid, infectious diarrheas, poliomyelitis and infectious jaundice, the technic for handling excreta is dependent upon available sewage disposal facilities If the hospital wastes enter a treated municipal sewerage system or properly functioning septic tank, bedpans may be emptied into hoppers or toilets without preliminary treatment Under other circumstances, stools should be broken up and emptied into a covered can containing a disin-
nated lime or five per
one hour before being
which is occasionally

here It is
l patients be
sently avail-
n the utility
room

Urine, vomitus, and liquid food wastes should be treated according to the same principles outlined for stools

Dressings, tongue blades, swabs, etc, should be discarded in paper bags which are then closed securely and placed in the refuse container for burning

Care of Dishes

Serving Food.—Taking care to remain "clean," the nurse or attendant may carry the tray to the patient's bedside table without donning a gown. If she assists the patient

she should carry out gown and handwashing technics as for other care.

Collecting Dishes and Trays.—It is good practice to sterilize all dishes from all patients. Although it is not necessary to have a special kitchen for dishes and trays from patients with communicable diseases, an area should be designated, in the regular kitchen, where trays and dishes from communicable disease patients can be prepared for sterilization. Wax paper bags or thick newspapers should be provided to receive solid food wastes and a pitcher or jar for liquid wastes.

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Dishes and trays should be placed directly in the dishwasher-sterilizer, if one is available or on the stove to boil for five minutes in a covered kettle. If it is not feasible to boil the trays, they may be thoroughly washed, rinsed in actively boiling water, and left to dry. Clean dishes and trays may be stored in the clean area of the kitchen. The use of paper plates, cups, tray cloths and napkins is becoming increasingly popular in communicable disease nursing, and the expense is compensated for in the economy of time and effort expended. Paper salt and pepper shakers, which are now available, eliminate another problem in isolation technic.

Care of Linen

The laundrying process in a modern hospital should be sufficiently thorough to render soiled linen free of pathogenic material in all but exceptional instances. In spite of the fact that all laundry receives the same treatment, it is common practice to process contaminated linen after so-called "clean" laundry has been finished. Under these circumstances special bags for contaminated linen are provided. Laundry chutes may be used with safety if bags are tightly closed.

Linen from individual patients may be collected in the discarded pillow cases or it may be tightly rolled into bundles. The "C D" laundry bag can be brought in the conveyor to the door of the room or unit to [illegible]

[illegible] She should, of course, wash her hands after this procedure.

All clothing and bedding used by persons being treated for anthrax, and possibly tetanus, should be sterilized by steam under pressure before being sent to the laundry.

Special Laundered masks should be autoclaved before being *re-issued for use*

Soiled diapers from all nurseries should be received in covered "step-on" cans in the nurseries The foot-controlled cover eliminates the possibility of hand contamination Diapers and nursery linen should, after laundering, be autoclaved before being returned to the nurseries Care should be taken to see that packages are small enough and the autoclave loosely enough packed so that actual sterilization takes place

Laundry Personnel – Laundry personnel should be protected by *the usual immunizations and should be instructed and supervised* in safe methods of handling all soiled linen

Care of Equipment

Thermometers should be washed with soap and water, with friction applied in a spiral, downward motion They should then be rinsed well and stored in a covered jar, either dry or in a solution such as Zepharin chloride (1 1000)

The following (and all similar articles) should be washed with soap and water, rinsed well and dried For those that may be damaged by soap and water, alcohol (70 per cent solution) may be substituted

- Flashlights
- Head mirrors
- Otoscopes
- Stethoscopes
- Toys
- Waterproof sheets and pillow slips

The following should be aired out of doors for several hours, in sun if possible

- Books (standing on edge, with pages separated)
- Mattresses
- Pillows
- Sand bags and the like

Any articles which may have been contaminated with spore-forming organisms should be subjected to sterilization by steam under pressure

Floors

Recent studies have shown that dust particles may be effective agents in the dissemination of pathogenic organisms and present

methods of floor care should be reviewed with this in mind Floors should never, under any circumstances, be dry swept Some hospitals use an oily sawdust-like preparation in sweeping Actual oiling of the floors is preferable because it provides a surface to which dust can adhere. Just enough oil (one gallon per 1000 square feet) should be used to leave a thin coating on the floor Care must be taken on hard surfaced floors lest any excess oil make walking hazardous Because only a thin film can be left with safety, the application will have to be repeated at intervals Most oil companies offer a special grade of floor oil which meets government standards concerning fire hazards and which is suitable for dust control purposes. Oiled floors should be cleaned only with clear, warm water No soap or alkali should be used

The practice of impregnating blankets, bedclothes and patients' gowns with mineral-oil-in-water, especially where dust-control measures are in operation for floors, provides another safeguard against the hazard of dust-borne pathogens

FURNITURE

Furniture should be damp-dusted, preferable with an oily solution Some metal furniture, particularly beds and bedside tables, may best be cared for by washing with soap and water

Maids and other auxiliary help should be as well instructed and supervised in their duties and responsibilities as are the professional workers in theirs. They should be specifically taught, by demonstration, how to avoid contamination and should not be allowed to start work until they have become skilled in hand-washing, and also in gown and mask technics if indicated

DUTIES OF AUXILIARY WORKERS

It has been found that, with careful instruction and adequate supervision, auxiliary workers can perform all purely housekeeping

sterilization

2 All general housekeeping activities in patient's rooms and cubicles.

3 Responsibility for seeing that ample supplies of soap, paper towels, paper bags, etc., are always available in patients' rooms, and kitchens

All clothing and bedding used by persons being treated for anthrax, and possibly tetanus, should be sterilized by steam under pressure before being sent to the laundry.

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The following should be aired out of doors for several hours, in sun if possible

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- Sand bags and the like.

Any articles which may have been contaminated with spore-forming organisms should be subjected to sterilization by steam under pressure.

Floors

Recent studies have shown that dust particles may be effective agents in the dissemination of pathogenic organisms and present

materials are placed in the proper receptacles, the hands should be washed again

Technics for the remainder of the day should follow the above pattern but it is not always necessary that the attendant wear a gown For instance, when refreshments are served, mouth temperatures

care is

faces.

dures

even when a gown need not be used

Certain procedures which are an integral part of diagnosis and treatment merit special mention These include blood pressure determination, clyses, infusions, transfusions, cultures, hypodermic injections and venipunctures All of these and any others may be carried out in the usual routine manner if thought is given before

A clean assistant may be needed

Receptacles for laboratory specimens must be kept clean on the outside

Discharge of Patient —The recovered patient should bathe, and dress in his own clothes Although he is to all intents and purposes no longer infectious, a separation between "clean" and contaminated must come somewhere and it is suggested that, when ready, he wait in a clean sheet

Terminal Disinfection

The room or cubicle should have a thorough cleaning and all equipment used by the patient should be subjected to the procedures outlined in section "Basic Procedures" The room should be aired and sunned, if possible for from 12 to 24 hours, before another patient is admitted

Visitors

Visiting patients with communicable disease is justified if the requirements of technic are maintained Since the restrictions thus imposed seriously detract from the pleasure and benefits of socialization, and since epidemiological considerations support the attitude, some institutions prohibit visiting In hospitals where it is permitted all visitors should wear gowns (a full length cape with

4. Responsibility for seeing that laundry bags are properly closed and sent to the laundry at proper intervals and that marked bags are in place for use at all times

5. Responsibility for seeing that soiled linen from the suspect and isolation nurseries is removed and taken to the laundry at proper intervals

6 Responsibility for wrapping nursery linen, masks and any special equipment for autoclaving

The role of the ambulance driver as an auxiliary worker who may be called upon to handle patients with communicable disease should not be overlooked

Admission, Daily Care, Special Procedures and Discharge

The stretcher pad should be covered entirely with a rubber sheet, and a cotton sheet should be placed over this Two additional sheets, a blanket, and a patient's gown should be sent out with the stretcher Attendants should wear gowns and masks when indicated The patient should be dressed in the hospital gown, wrapped in one sheet and the blanket and placed on the stretcher The attendant should then wash his hands and cover patient and stretcher with the second clean sheet A small child can be wrapped as completely as possible in a clean sheet, which has first been draped over the attendant's arms, and carried to the ambulance Upon arrival at the hospital, the patient should be taken directly to his room or cubicle The stretcher and equipment used should be properly disinfected and the interior of the ambulance should be washed with soap and water if it has actually become contaminated It should always be aired before it is used again

Admission.—All necessary personal equipment for the patient should have been assembled in the room or cubicle in preparation for his admission Attention should be given again to the provision

that will be needed (water, tissues, clean linen, paper bags, etc) should be taken into the room or cubicle Gown, and mask if indicated, should then be donned When care has been given and the fluid waste, refuse, and laundry prepared for final disposal, the hands are washed and the gown and mask removed Taking care not to contaminate her clothing and touching nothing en route, the nurse or attendant should take the soiled linen and waste

As soon as the needle is inserted the nurse removes the cotton from Test tube No. 1 and places it on the sterile cover. After flaming the mouth she hands the test tube to the doctor who grasps it with a sterile holder. When the specimen is obtained, the nurse receives the test tube in an alcohol wipe, flames the mouth, replaces the cork and wipes the outside before returning it to the rack. This process is repeated until the desired number of specimens is secured.

When a spinal manometer is used, the nurse connects the adaptor to the needle and holds it in place until the pressure is read, after which she disconnects it with an alcohol sponge

The doctor cleanses the site of the puncture with alcohol, then with dry cotton, and applies a sterile dressing and adhesive plaster

After the procedure is completed the needle is placed in alcohol

the dressing room

Administration of Antitoxin

Before administering any animal preparation, intracutaneous and ophthalmic sensitivity tests are always done by the doctor For these a 1 0 ml. syringe with a 27-gauge needle containing a 1-100 dilution of horse serum is used If with this dilution the tests are at all questionable they should be repeated using a one-to-ten dilution of the serum

The antitoxin to be given is warmed to body temperature in a bowl of warm water and, following a negative reading of the sensitivity tests, is drawn into the syringe in the presence of the doctor The site of injection is cleansed with iodine and alcohol by the doctor, after which the antitoxin is slowly injected intramuscularly or intravenously. Small children must be restrained The rate of administration is accurately times

A hypodermic syringe with 1 ml of epinephrine solution 1/1000 and a rubber tourniquet must be in readiness Some authorities

hypodermic syringe with the epinephrine is kept at the bedside for emergency use.

If the skin sensitivity test is positive, the antitoxin may be given by the doctor in fractional doses at intervals of twenty to thirty

head opening works well) and be carefully instructed as to precautions. They should be seated at least five feet away from the patient. It should be emphasized that any plan for visitor control will require constant supervision by all personnel on duty during visiting hours.

In general, long and frequent visits to patients with communicable diseases should be discouraged. Individual exceptions either prohibiting visitors or allowing more intimate visitor-patient contact will have to be made from time to time on the basis of important needs of the patient, the nature of his disease, and the comprehension and co-operation of the visitor.

Procedures

The following technics and procedures are modified from the Manual of Medical Aseptic Technic and Procedures of The Willard Parker Hospital, 1952.

Lumbar Puncture.

Equipment:

- Iodine, 3 per cent
- Alcohol, 70 per cent
- Local anesthetic
- 2 ml. syringe.
- Hypodermic needles.
- Sterile medicine glass.
- Two sterile lumbar puncture needles in test tubes
- Three sterile test tubes for separate specimens of spinal fluid
- Test-tube rack
- Sterile test-tube holder
- Spinal manometer
- Two pairs of sterile gloves
- Sterile towels and fenestrated sheet (in package)
- Sterile cotton
- Sterile gauze (2 inches by 2 inches)
- Adhesive strips.
- Alcohol lamp and matches
- Kidney basin for gravity set and holder.
- Container of green soap and alcohol for used needles

An assistant holds the patient in position on the ward carrier

Spectacles to protect eyes
Masks
Lower shelf, deep tray with 5 per cent Lysol solution for contaminated equipment.
Kidney basin with 70 per cent alcohol for light carriers
[illegible]

Low stool.

A "clean" nurse assists as may be necessary with suction, cultures, etc.

A nurse gowned carries the child to the admitting room and places him on the treatment table to be examined by the doctor

When the doctor is ready to proceed, a *mummy* restraint is ap- [illegible]

under the body The opposite side of the sheet is then drawn over the left arm, pulled tightly across the chest and pinned about 2 inches below the right shoulder A second safety-pin is fastened at the level of the wrist to immobilize the arms The lower right portion of the sheet is now tucked securely under the extremities, the left is mitred above the knees, pulled tightly around the extremities and pinned to a fold in the dart

Laryngoscopy and Suction

The doctor, with mask and spectacles adjusted, sits on a low stool at the head of the table The necessary articles are arranged on the small stand with the suction apparatus The clean nurse hands the doctor the proper sized laryngoscope, tongue depressor and suction tip The patient's shoulders are placed on the sandbag with the head dropped back in the mid-line The contaminated nurse leans across the patient's chest and grasps the head firmly, placing the palms of her hands on the sides with fingers extended and thumbs on the forehead A slight turn of the patient's head backward permits a more direct view of the larynx. Two nurses may be needed to restrain the child completely.

minutes The nurse remains with the patient until the series is completed If the eye test shows inflammation, the doctor will instill a drop or two of a 1:1000 solution of epinephrine to neutralize the reaction, and the antitoxin, if it is definitely indicated, is given in fractional doses

Tube-room Technic

The admitting room on the diphtheria floor is equipped for laryngoscopy, suction, intubation, extubation and tracheotomy as follows:

Treatment table provided with
- Rubber covered foundation.
- Large sheet
- Crib sheet for mummy restraint
- Sandbag with removable cover.
- Three safety-pins
- Dry cell batteries with rheostat and cord attachment for laryngoscope light

Small stand equipped with·
- Suction machine with rubber connecting tube and suitable adapter for metal suction tip, rubber connecting tube for spray supplied with a stop-cock.
- Small bowl of water to test suction.
- Paper bag for waste (pinned to the table).

Table supplied with.
- Intubators of various sizes (indirect) top shelf
- O'Dwyer tubes with linen thread attached.
- Direct intubators
- Indirect extubators
- *Direct extubators*
- Metal gauge for measuring intubation tubes
- Large glass jar with gauze squares, lower shelf.

[illegible] and suction

[illegible]

- Metal tongue depressor.
- Hemostats with sterile laryngoscopic applicators attached
- Scissors.
- Metal suction tips (various sizes).
- Jar with sterile cotton applicators in tube containers
- Adrenalin 1 to 1000.
- Ephedrine, 3 per cent.

A kidney basin is placed at the foot of the table to receive contaminated articles. The suction apparatus with soft rubber catheter attached is in readiness

A "clean" nurse assists the doctor as needed. The doctor cuts the tapes attached to the tracheotomy tube, discards it in the kidney basin provided, after which the clean nurse hands the doctor alcohol compresses, dry compresses and mercurochrome With the obturator in place, the nurse wets the tip of the tracheotomy tube with sterile saline and hands the tube with tapes and dressing attached to the doctor. After inserting the tube, the doctor discards the obturator and adjusts the tapes The nurse hands the doctor the inner tube

Upon completion of the procedure, the contaminated nurse removes the restraint and takes the patient to the cubicle The "clean" nurse is responsible for leaving the admitting room in order and preparing the tracheotomy tube and dressing for subsequent use

Care of a Patient with Tracheotomy

Equipment
- Container of sterile catheters, each with several openings near tip
- Container for used catheters

suctions

gives oxygen for cyanosis or as ordered by the doctor, by holding the oxygen funnel close over the tracheotomy tube

The tracheotomy tube is cleaned as ordered or whenever the airway is bubbling with mucus The inner tube is removed and placed in the basin of saline solution Three to five drops of sterile saline are instilled in the outer tracheotomy tube and at once suctioned out If suction of the trachea itself is necessary, with the suction pump in operation, the tube is pinched, then passed in the tracheotomy tube into the trachea a shorter or longer distance as indicated, then unpinched and withdrawn with a slight rotary motion Or a "Y"-shaped glass tube may be included in the suction circuit with one point of the tube open while the suction tubing is being inserted in the trachea A finger tip placed on the open end of the "Y" then permits suction as the tubing is withdrawn

The doctor now laryngoscopes the patient, applies suction if necessary, and afterwards takes the cultures. The ephedrine spray or adrenalin applicators may be applied. Immediately upon removal of the laryngoscope, the nurse turns the child on his side and with some gauze squares wipes out the mouth The child is placed flat on the table and the restraint loosened.

After each treatment the doctor places the instruments in the Lysol solution and the light carrier and the spectacles in the basin of alcohol Later all contaminated equipment with the exception of the light carrier is washed and then boiled. The light carrier is wiped with 70 per cent alcohol Masks are placed in the basin of soap solution, later washed, and returned to the Central Supply Room The "clean" nurse is responsible for leaving the room in order

Care of the Suction Apparatus —The suction apparatus is cleaned by flushing the connecting tubing with water The bottle with the return flow is emptied into the hopper and rinsed If any outer surfaces of the apparatus become contaminated, they are wiped with 70 per cent alcohol

Intubation —When intubation is done, the patient is placed on the table, a *mummy* restraint applied by the nurse and the mouth gag adjusted by the doctor The contaminated nurse holds the head from above while the doctor at the right side of the patient inserts an O'Dwyer tube When the tube is in place, the doctor cuts the linen thread and discards it As soon as possible the restraint is removed

Extubation.—Either the direct or indirect method of extubation is employed For the former, the following articles are needed

Proper sized laryngoscope
Tongue depressor
Gauze squares
Wire extubator or laryngoscope forceps
Suction equipment if necessary

For the indirect method, an extubator, mouth gag and gauze are needed . . . .

Inner tube
Tracheal dilator.
Compresses

Unsterile articles as needed alcohol, 70 per cent, and mercurochrome

When the patient's tracheotomy tube is changed a gowned nurse carries the patient to the admitting room and places him flat on the treatment table A *mummy* restraint is applied if necessary.

Nurses reporting for duty at the Willard Parker Hospital had to be immune to diphtheria as demonstrated by a negative Schick test. Nurses were required to have had a successful smallpox vaccination within two years, one triple typhoid vaccine must have been given within the same period. Chest x-ray examinations were also required.

MANAGEMENT IN BOARDING-SCHOOLS AND SIMILAR INSTITUTIONS

Boarding-schools present peculiar difficulties in the proper management of contagious diseases. Recognizing this, the School Physicians Association, a former organization of the school physicians of most of the leading boarding-schools and private day schools of the East, appointed a committee consisting of Dr. Haven Emerson, Professor of Public Health Administration in Columbia University, Chairman; Dr. Samuel T. Nicholson, Jr., then School Physician of The Hill School; and Dr. Philip M. Stimson, to draw up a procedure for the prevention and control of epidemics in boarding-schools. The report of this committee was approved by the School Physicians Association on November 2, 1928, and the measures recommended have been followed in a number of the leading boarding-schools of the eastern states. It is submitted herewith in the belief that with due consideration of the modern use of the antibiotics, the measures recommended are still suitable and can be adapted for the handling of epidemics in almost any institution similar in nature to a boarding-school.

Procedure for Prevention and Control of Epidemics in Boarding-schools

In considering the following sections, one must be fully aware of the impracticability, under various conditions found in boarding-schools, of carrying out in their completeness each and all of the precautions and procedures offered as part of an ideal plan.

COMMENT ON MEDICAL ASEPTIC TECHNIC

Following the installation of medical aseptic technic and individual isolation at the Willard Parker Hospital beginning about 1926, there was a decrease in cross-infections, complications, deaths, and average stay in hospital all to a greater degree than could be attributed to conditions existing outside the hospital. For instance it was felt that a decrease in the average hospital stay of measles patients from sixteen to ten days was primarily due to the installation of individual isolation. The hospital mortality for all contagious diseases dropped steadily from 5 6 per cent in 1929 and higher before then to 1.5 per cent in 1937, 1 2 per cent in 1938, and 1 3 per cent in 1939, but many factors besides medical aseptic technic contributed to this improvement More recently the use of the sulfonamides and the antibiotics has further lowered the rate to 1 0 per cent in 1945, and 0.4% in 1952.

To carry out an adequate medical aseptic technic in a ward, pavilion, or entire hospital, the services of at least 2 nurses or nurses' aides for each 3 patients are desirable When fewer nurses than in this proportion are provided, cross-infections, complications, and deaths are apt to increase, and in addition this expensive hospitalization of patients will be unnecessarily prolonged.

A hospital cannot be held responsible for the cross-infections (or second diseases) which are due to exposure before admission But for each such "outside exposure" there should be far fewer than two cross-infections due to "inside exposure." When the hospital census exceeds 80 per cent of the bed capacity, or when the nurse to patient ratio falls below 1 to 3, it is difficult to prevent cross infections due to exposure after admission

Effective technic also requires that the porters and ward maids be well trained in their parts of the technic and be cooperative and reliable. At the Willard Parker Hospital, they were given regular classes, and they participated in frequent demonstrations.

3. All persons engaged in a teaching capacity or in the preparation or serving of food should be medically examined before they are employed, and annually thereafter, and all such persons should be inspected by the school physician before returning to duty after any illness, and after absence on vacation.

4. The washing of all eating and cooking utensils should be so carried out that the various articles are sterilized in the process after each meal.

5. The washing of sheets, pillow-cases, towels, and the pupil's clothing should include boiling during the process

6. Record should be made and kept up to date from the time the pupil is registered in the school, of susceptibility or immunity to the major communicable diseases The determination of susceptibility should be by specific skin reactions, where these are practicable, to supplement the history of previous occurrences of any of the communicable diseases Susceptibility to diphtheria should be determined and certified to by a physician before a pupil is accepted at the school Typhoid vaccination should be offered and advised Successful vaccination against smallpox within five years should be required on admission

7. The younger pupils, that is up to the age of twelve or thirteen years, should be kept separate so far as practicable in class, study-room, assembly, and dining-room from the pupils of older ages.

C. Measures Applicable at Times of Special Hazard, or When an Epidemic Threatens or is Under Way

1. On declaration by the school physician that an outbreak of communicable disease is threatened, arrangements should be made as promptly as possible to space out the pupils, as far as practicable, for the sake of increasing the distance between pupils in sleeping, class, dining-room, assembly, chapel, gymnasium, or other places within the school. In this connection it is advised that two or more

A school community must be considered with the same understanding of the *limiting factors of time, personnel*, cost, etc , that is applied in deciding a course of conduct for an individual to pursue when needing preventive or curative medical direction

For the group as for the individual, what is the ideal to be approached is recommended, although it may be found impracticable of application under the conditions presenting themselves at the moment.

A. Definition and Scope

By the term epidemic we mean the occurrence of one or more cases of a major communicable disease in a large susceptible group, especially when the distribution of the first cases includes different age groups among school children.

For the purpose of the present report the discussion of procedures will be limited to those applicable to communicable diseases which are transmitted chiefly or solely through the discharges of the mucous membrane of the respiratory tract and its accessory sinuses

B. Factors in the Housing, Personnel, and Management of Boarding-schools which can be Relied upon to Reduce the Hazards of Epidemic Prevalence of Communicable Disease

1 Each pupil should have a room or cubicle space to himself for sleeping (*Sixty square feet of floor space with window.*) When 2 or more pupils are provided for in one room or cubicle space, the beds should be not less than 6 feet apart on centers and the positions of the beds should be determined by the school physician.

2. Unless the water and milk supplies are regularly tested for sanitary quality by adequate public authority, the testing should be carried out periodically under the direction of the school physician and reports given to him weekly or monthly.

It is commonly as important to maintain isolation technic and procedure for the purpose of protecting each bed patient against secondary or complicating infection from other patients, as it is to separate the sick from the well

By observation is meant such clinical and administrative supervision as will insure the earliest detection of evidences of communicability, by the use of daily inspection, or the taking of nose and throat cultures, or the keeping of temperature records, and will at the same time determine the adequacy of precautions designed to prevent secondary cases or complicating infections

8. Where indicated, cultures should be made from the nose and throat of pupils and other school personnel, especially teachers and those persons dealing with the preparation and serving of food, and individuals who show the presence of a causative organism should be isolated for purposes of observation.

9 Provision should be made for an ample convalescent period, and subsequent return to school only on the evidence of negative cultures when a specific organism is determined to be the cause of the epidemic, and after approval by the school physician, this to apply to teachers and school personnel as well as to pupils

10. The return to school of contacts, suspects, and carriers should be governed by accepted public health practice at the discretion of the school physician.

11. The possible source of infection should be sought with the object of preventing additional cases or recrudescence of the outbreak.

12 Under certain conditions, a form, or grade, dormitory or other group, or even the entire school should be closed by sending home or to other suitable care the pupils not yet infected but susceptible, and by permitting those who have recovered sufficiently, to spend a further convalescent period elsewhere than at the school.

Closing of a school and the wide distribution of exposed susceptibles to their homes, by public conveyance or other-

seatings at meals be arranged for, instead of one sitting in the dining-room, which is usually just capable of providing for the entire school enrollment at one sitting.

2 During the epidemic period, weekend absences from the school should be discontinued, and all occasions for assembling indoors with persons, particularly other groups of young people from outside the school community, as at dances, indoor athletic, musical or other festivities or competitions, should be discouraged

3. An added hour of sleep should be arranged for the older pupils, daily, and if practicable two hours additional daily for the younger pupils, attention being paid to the time when the pupils are in bed with lights out.

4 Less scholastic work should be required of the pupils, extracurricular activities should be reduced, and all assemblages should be temporarily discontinued, including chapel.

5. More circulation of air should be provided in classrooms, dining-rooms, and halls, where the day's routine requires the gathering of pupils

6. The use of the swimming-pool should be carefully limited to persons wholly free from any symptoms of catarrhal or other inflammations, acute or chronic, of the nose, throat, ears, or skin, and if the epidemic disease is widely distributed throughout the school or the common cold is prevalent, the swimming-pool should be closed temporarily

7. All cases, suspects, contacts, and convalescents of a communicable disease should be kept under such form of isolation or observation as is appropriate for each category, as determined by the school physician and according to bacteriological and other evidence of communicability. Severe and mild cases should be separately isolated in rooms or cubicles in an infirmary.

By isolation is meant separation physically and through aseptic medical and nursing technic so that neither direct nor intermediate transmission of infectious material can occur from the sick to susceptible persons.

membranes, such as a fresh cold, a red or painful throat, a running nose, repeated sneezing or coughing, and red or inflamed eyes

4 Nausea and vomiting

5. Swelling or tenderness, such as of the cheeks or the glands of the neck.

6. Chills or convulsions

7. Any other distinct change from the usual appearance and behavior of the child.

II There should be constantly in attendance during the school hours someone with knowledge, judgment, and authority, who may pass on each case as it arises When the school is small and cannot afford a doctor for this purpose, the health supervisor, be it nurse or teacher, should be carefully trained, and in case of doubt should take no chances

III. Records for each pupil should be available, showing among other facts the contagious diseases which have been suffered and the inoculations which have been received, that is, which pupils are to be considered immune or susceptible to any given disease Such a record of each class group is essential for the proper management of a classroom exposure

IV. There should be definite regulations covering action in the cases; (1) of children who have been absent from school because of a contagious disease and who are to be considered for readmission; (2) of the other children in the family of contagious patients, both those who are immune and those who are susceptible, (3) of children exposed outside of school but not in the home, and finally of children who have been exposed in school. The steps taken will vary under different circumstances, and particularly in the different diseases.

For children who have been absent from school because of an attack of a contagious disease, the regulations of the local health authorities will hold Similarly children in the patient's family are usually controlled by the local regulations In many communities the health authorities have

wise, should be done if found necessary, only with the knowledge and consent of the local or state health officer, who should be informed promptly of the development of cases of any one of the notifiable diseases.

Conditions which may justify closing a school or vacating a dormitory or distributing a class or form to their homes include· continued development of secondary cases after apparently adequate isolation of primary cases; the presence of a high proportion of susceptibles in the exposed group; inadequate infirmary facilities for isolation and medical care of an increasing number of patients

MANAGEMENT OF CONTAGIOUS DISEASES IN DAY-SCHOOLS

An effective scheme for the control of contagious diseases in day-schools must include a recognition and adoption of the following plans and measures.

I. Some plan or program should be in effect by which all pupils suffering from any variation from normal health are immediately removed from contact with their classmates, and are kept isolated until it can be demonstrated that it is safe to allow them to mingle with their fellows again This is particularly important in cases involving the upper respiratory tract, such as fresh colds. This program should include not only *arrangements for separation of the ill child* from the rest of the children, but also first-aid, and a decision as to whether the child may remain in school or should be sent home, and in the latter instance, notification of the parents, and the transference to them of the responsibility for the child's future care. Symptoms the appearance of which should warrant the separation of the child from his classmates and a thorough examination, preferably by a doctor, include *the following:*

1. Unusual pallor or flushing of the face.
2. Any unusual apathy, also faintness or dizziness.
3. Any evidence *of inflammation of the respiratory* mucous

They may use the same washrooms as other children, but at different times. They are also inspected daily by the school health officer. This procedure is also permissible in certain instances of exposure to even such serious diseases as diphtheria and scarlet fever, because classroom exposures to these two diseases are rarely followed by secondary cases.

In the case of measles, chickenpox and whooping cough, all very contagious diseases, a choice will have to be made between two types of segregation, the above, with its probability that a child who is in the early and unrecognized stages of a disease, may attend school, and thereby reexpose the classroom, and the other, the definite exclusion of all those children who have not already had the disease in question, for the full period of danger There may be occasions when it will seem wise to close a classroom entirely for the duration of the incubation period of the disease in question During the period a classroom is closed, it should be thoroughly cleaned, sunned, and aired Textbooks should be left open *in the sun for six hours Everything washable should be* washed with soap and water

And finally, no scheme for the control of communicable diseases in a day-school can hope to be effective without an active campaign of education wherein the pupil is taught how to protect himself from infection, and how to protect others when himself sick, wherein the teachers are taught how to watch for the first signs of illness and to act promptly, and wherein the parents are taught the value of cooperation with the school's health authorities, and of absolute obedience to the school's health rules For example, if parents can be made to realize that a child below par is unusually susceptible to contagion, and if exposed would be the one in the class most liable to contract a contagious disease, they will be far more willing to keep the child home until quite well.

First generation cases of a contagious disease, or those contracted outside school, obviously cannot be avoided by the school authorities, nor can their exposing the school be always avoided

no regulations regarding contacts to such minor diseases as rubella, chickenpox, and mumps, but school health authorities would do well to exclude from the school during the period when they are liable to come down with the first symptoms, those susceptible children who have been exposed at home to these diseases. It is not fair to the rest of the pupils to run the risk of introducing the disease into the school, and particularly in the case of chickenpox, the likelihood of secondary cases occurring in the other children in the family is very high.

For children exposed outside of school but not in the home, the likelihood of secondary infections is not as strong as when the contact is the intimate one of home life. Accordingly, each case will have to be decided on its merits, but in the lesser diseases it will frequently be felt justifiable to allow the child to attend school, provided that he is carefully watched both at home and in school for any possible signs of illness

For schoolroom exposures to the less serious diseases such as mumps and rubella, it is hardly ever necessary either to close the classroom or to exclude any children from school attendance Where the exposure is slight it is often sufficient to notify the parents of the exposure and urge their cooperation in keeping away from school a child who shows any signs of ill health The susceptible children who attend school should be watched carefully by the school health authorities, and should be inspected at least twice during school hours each day. For their own welfare also, parents should know when there is the possibility of either mumps or rubella developing in their children

Where the classroom exposure is fairly strong but the disease mild, segregation of the pupils of the room is desirable. In carrying out this measure the children do not arrive and depart from the school at the same time as the children in the rest of the classrooms They have a separate recess period, and attend no exercises in which the rest of the school participates. They use their own classroom only.

are presumably susceptible so that they may be given protection by suitable inoculations or medication Unless the susceptibles have already been so fully exposed as to be quite certain to come down with the disease, as in the case of chickenpox, their removal from the home may be indicated

The unit of isolation of the patient should be well defined and considerable care is sometimes necessary in its selection It may consist of a room with or without a bathroom, or one-half a room, or perhaps the whole home. There must be a definite understanding of the limits of the contaminated area comprising the unit Where the unit is a room, the doorway is an easily remembered boundary, but sometimes it seems necessary to tack a sheet across the door as a more vivid reminder of the presence of contamination inside the room. When a part of a room comprises the unit, as in a case where a mother or nurse is sharing a bedroom with a sick infant, a screen may comprise the boundary, or a mere chalk line on the floor may suffice Whatever the extent of the contaminated unit, the patient must be confined within it together with his entire equipment

The attendant of the patient may be the mother or a nurse, but preferably not both at the same time The smaller the number of people entering a contaminated area, the fewer are the chances of the spread of the contagion Hence, visitors to the patient should be kept at a minimum When the attendant and the physician enter the contaminated area, and if there is any likelihood of their clothes touching a contaminated object, they should wear a gown, which when not in use should be hung up, preferably in a dry, sunny, but convenient location

Concurrent disinfection of contaminated people and objects that are to leave the unit is, of course, essential In order to leave the unit the attendant should unfasten the gown, push up the sleeves, wash the hands, slip the gown off without touching the outside of the gown, hang it up, and finish washing. The doctor's technic will vary somewhat with the circumstances. Before entering the unit he should have removed

Hence, second generation cases, or those due to school exposure to a first generation case, cannot all be forestalled—but most of them should be avoided

And all second generation cases should be prevented from causing third generation cases. Under most circumstances, the existence of a third generation case shows inadequate school health supervision.

MANAGEMENT OF CONTAGIOUS DISEASES IN THE HOME

In making the arrangements for managing a contagious disease in a private home, there must be considerable variation in the exactness and severity of the details depending on the nature of the home and the household, and likewise on the particular disease When the disease is usually trivial, such as rubella or mumps, and there are no susceptible persons in the home, a certain degree of laxity of isolation may be permissible Cleanliness, however, should be stressed, particularly in the case of another member of the household who wishes to go in and out of the home When the disease is a more serious one, such as diphtheria or there are others in the household who must be protected such as premature infants, or children with eczema or chronic illness, efforts should be made to approximate as closely as possible the exact technic the general principles of which are described in the section on Management of Contagion in a Hospital

The nature of the technic to be established will thus depend somewhat on an examination of the rest of the household It is certainly useless to isolate rigidly an obvious case of some contagious disease when some other member of the home is allowed to go and come while suffering from the same disease, perhaps in a very mild form, or while acting as a healthy carrier of *the infection. Accordingly each person in* the household should be examined to rule out mild cases of the infection, and if possible to detect any possible carriers Furthermore, an identification should be made of those who

are presumably susceptible so that they may be given protection by suitable inoculations or medication. Unless the susceptibles have already been so fully exposed as to be quite certain to come down with the disease, as in the case of chickenpox, their removal from the home may be indicated

The unit of isolation of the patient should be well defined and considerable care is sometimes necessary in its selection. It may consist of a room with or without a bathroom, or one-half a room, or perhaps the whole home. There must be a definite understanding of the limits of the contaminated area comprising the unit. Where the unit is a room, the doorway is an easily remembered boundary, but sometimes it seems necessary to tack a sheet across the door as a more vivid reminder of the presence of contamination inside the room. When a part of a room comprises the unit, as in a case where a mother or nurse is sharing a bedroom with a sick infant, a screen may comprise the boundary, or a mere chalk line on the floor may suffice Whatever the extent of the contaminated unit, the patient must be confined within it together with his entire equipment

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Concurrent disinfection of contaminated people and objects that are to leave the unit is, of course, essential In order to leave the unit the attendant should unfasten the gown, push up the sleeves, wash the hands, slip the gown off without touching the outside of the gown, hang it up, and finish washing The doctor's technic will vary somewhat with the circumstances. Before entering the unit he should have removed

his coat and wrist-watch, rolled his sleeves above the elbow, scrubbed his hands to prevent carrying an infection to the patient, and taken from his bag only such instruments as he will need *On entering the unit, if skillful, he may be able* to do the necessary examinations with a minimum of contagion of his hands and the instruments, and without contaminating his clothes, although not wearing a gown. For certain diseases such as diphtheria it is desirable for the doctor to wear a gown At the end of the examination, the doctor should take off the gown and wash his hands and forearms thoroughly, while his instruments should be cleaned with soap and water and sponged with alcohol If hung up in the sunshine until the doctor calls the next day, his gown can at that time be considered clean again unless it had been grossly contaminated by moist excretions

Concurrent disinfection of articles requires systematic thought and planning, but can be easily accomplished in most homes The patient's dishes should be put in a boiler conveniently placed just outside the contaminated area, and then boiled for fifteen minutes. Refuse of food, paper towels, and the like, should be collected in a paper bag in the contaminated area This paper bag, the outside of which is contaminated, may be slipped into a larger and cleaner bag or wrapped in a clean newspaper and then the whole burned. If there is a fireplace, an open fire simplifies greatly the disposal of such contaminated inflammables. Bed linen, towels, and underclothing should be boiled in a clothes-boiler before they are washed If care is observed a bathroom may be used by a patient or the attendant without contaminating it or making it unwise for the rest of the family to use it also With the help of paper towels, a pile of which should be handy, a contaminated person can do many things, such as turn on a clean faucet, without contaminating anything but the paper towel which is then put in the refuse bag. Paper covers can be used for protecting the toilet seat, and if the bathtub is used by a contaminated person it can be immediately disinfected by scrubbing with

soap and water. The patient's own cloth towels should, of course, be hung inside the contaminated unit.

At the end of the isolation period when the patient is to be released from the restrictions of the unit, terminal disinfection of the patient and of the unit should be done The patient should be given a thorough bath and shampoo, should be wiped with clean towels and dressed in clean clothing in a clean area. Inasmuch as after the conclusion of isolation particularly for scarlet fever, there still is a slight possibility of the patient's being able to transmit the disease to susceptible people, semi-precautions should be followed for a number of days thereafter The patient should not kiss susceptible people on the mouth, nor associate too intimately with them, such as sleep in the same bed with another child

Finally, disinfection of the contaminated area consists, in simple words, of a "spring cleaning" Particular attention should be paid to articles that the patient is known to have touched and those within 5 feet of the patient's head More distant articles in the contaminated unit, such as curtains on the other side of the room, need not have such particular care Anything that can be washed, such as the bedstead, the furniture, and the floor, should be washed thoroughly with soap and water Fuzzy toys, old books, and refuse should be burned The mattress, pillows, rugs, drapes, and good books should be hung in the sun and fresh air for at least six hours, preferably on each of two days, and finally the entire room should be sunned and aired for twenty-four hours This process of disinfection is much more effective than fumigation, which is no longer advocated

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GLOSSARY

A

aerobic. Requiring free oxygen for growth

agglutinin. A specific antibody capable of causing the clumping of the bacteria peculiar to a disease (See page 25.)

agranulocytosis. An acute disease characterized by a marked diminution of granular leukocytes in the blood and a resulting poor resistance to acute infection.

allergy. A state of altered reaction to foreign protein.

amboceptor. An intermediary which enables complement to be effective. (See page 26.)

anaerobic. Requiring practically complete exclusion of free oxygen for growth

anaphylaxis. A reaction of hypersensitiveness due to the union in a patient of a foreign protein with antibodies produced by a previous introduction of the same protein. (See page 40.)

angina. Any disease, but particularly one of the fauces, attended by a sense of strangling pain or suffocation (See page 152.)

anorexia Loss of appetite.

antibiotic A compound or group of compounds produced by a microorganism which destroys or retards the multiplication of other microorganisms.

antibody A specific constituent or property of the blood and tissue fluids of an immune being, antagonistic to a pathogenic microörganism or its products. (See page 25.)

antigen A substance that can cause the formation of an antibody in the blood and tissue fluids (See page 25.)

antitoxin. A neutralizer of toxin; a property in blood serum which is resistant to, or counteracts, toxin. (See page 38.)

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clean. Known not to be contaminated. (See page 555.)

clinical manifestations. The symptoms and signs of an abnormal state of health

communicable. Capable of transmission from one individual to another. Direct contact is not necessary (See page 17.)

complement A substance found in serum and cell which acts in conjunction with an amboceptor in causing lysis (See page 25.)

contact. A person or animal who is known or presumed to have become contaminated.

contagious disease An infectious disease that is spread or contracted as the result of direct contact (See page 17)

contamination. The presence, actual or presumed, of pathogenic microorganisms or viruses (See pages 555, 560)

convalescence The period of the restoration of health after disease

crisis A sudden drop in fever, or in the severity of the symptoms of an infectious disease

croup Any affection of the larynx or trachea causing a hoarse hollow cough and difficult stridulous breathing (See page 105.) Infection due to the diphtheria bacillus or a streptococcus, and exudate forming a false membrane are usually present. **false croup.** A temporary spasmodic affection of the larynx with slight inflammation only, and no false membrane, but causing symptoms suggesting true croup.

cyanosis. A bluish discoloration of the skin resulting from deficient oxidation of the blood

D

defervescence The disappearance or cessation of fever. (See page 34.)

desquamation The shedding or peeling of the superficial epithelium, as of the skin or mucous membranes.

Dick test. The test for susceptibility to scarlet fever. (See page 172)

aseptic technic, medical. An exact technic for the proper management of contagious diseases. (See page 554.)

atopen. An antigen that causes an atopic reaction.

atopy. *The state of being naturally hypersensitive to a* foreign protein. This state is dependent on a hereditary influence. (See page 39.)

attenuation. *The weakening of the virulence of a micro-*organism or virus. (See page 24.)

B

Babinski's reflex. (Not "sign") Dorsal extension of the great toe on stroking sole of foot—present normally to age of twelve to fourteen months, and with lesions of pyramidal tract.

bacteriemia. The presence in the blood of bacteria, but only as a subsidiary feature of the clinical condition.

bacteriolysin. A specific property of the blood and tissue fluids capable of causing the disintegration of a given microorganism (See page 25.)

Brudzinski's contralateral leg-reflex *With the patient supine,* forced flexion of one knee onto the abdomen causes the other hip and knee to be flexed. Present in various neurological conditions

Brudzinski's neck sign With the patient supine, forced flexion of the head causes flexion of the knees, and evidences of discomfort. Usually considered indicative of meningeal irritation. (See page 400.)

bulla. A skin-vesicle filled with fluid, a blister or bleb.

C

carriers. Those who while not necessarily showing signs or symptoms of a disease, harbor and eliminate its specific microorganisms or viruses, and so are potential sources of contagion.

cilia. Hair-like appendages on certain epithelial cells the function of which is to move extraneous particles.

H

heterophile agglutination The increased power for the agglutination of sheep's red blood corpuscles found in the inactivated blood serum of certain patients (*e g.* those with infectious mononucleosis. See page 25).

humoral. Pertaining to the body fluids

hydrocephalus. Increase in the fluid content of the head, with resulting increase in the size of the head (See page 402.)

hyperesthesia. A state of excessive sensibility.

hyperimmune serum. The serum of a person who has had a given disease and also subsequent inoculations against that disease, *e g.*, whooping cough followed by vaccination with pertussis vaccine

I

idiopathic Not preceded by any other disease; of spontaneous or unknown origin.

immunity. Resistance against infections (See page 24)

incubation period. The period of time elapsing between exposure or inoculation and the onset of symptoms. (See page 33)

infection. The process resulting from the invasion and proliferation of microorganisms or viruses in tissues beneath the surface (See page 17.) **secondary infection.** An infection of a patient already having a different infection **cross infection** An infection of a patient, usually in a hospital, with a disease other than that for which he was admitted.

infectious disease. A disease caused by a living transmissible agent. (See page 17)

inoculation. The intentional introduction into the body, of the virus or microorganism causative of a disease

intrathecal Within the meninges

intubate. To insert a tube, particularly in the larynx.

discrete. Separated, in distinction from confluent.

disinfection. The destruction of the viability of pathogenic microorganisms by physical or chemical means. *Concurrent disinfection* is the immediate destruction of infectious material discharged by the patient, and the immediate sterilization of articles and persons contaminated by such discharges

dysfunction. Difficult, or abnormal function.

E

enanthem. An eruption on a mucous membrane in distinction from exanthem. (See page 35.)

endemic. The fairly constant presence of a disease in the inhabitants of a given area.

endotoxin A toxin which is retained in the body of a microorganism and is liberated upon the disintegration of that organism (See page 22.)

epidemic. The presence of a disease in sudden great increase over the average incidence.

erythema. A redness or congestion of the skin.

erythrogenic. Producing red (Refers to corpuscles or to rash.)

etiology. The summation of all the factors relative to the cause of the presence of a disease.

exanthem. 1. An eruption upon the skin 2. Any eruptive or exanthematous disease (See page 35.)

exotoxin. An extracellular toxin existing outside the cell body of the microörganism

extubate. To remove a tube, as from the larynx or trachea

F

fastigium. The height or climax of a disease. (See page 34.)

flaccid (flak-sid) Soft, flabby, relaxed.

filtrable. Capable of passing through a filter.

Froin's syndrome. *The spinal fluid is yellow and coagulates* rapidly.

H

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inoculation The intentional introduction into the body, of the virus or microörganism causative of a disease

intrathecal Within the meninges.

intubate. To insert a tube, particularly in the larynx

invasion. The onset, or manner of attack, of a disease.
in vitro. In glass; that is, in a test tube
in vivo. In the living person or animal.
isolation. The separation from other persons of an individual ill with a contagious disease or otherwise known *to be a carrier of the causative agent thereof.* *(See page 555.)*

K

Kernig's sign. With the patient supine and leg flexed at right angles at both hip and knee, forced extension of the knee is resisted, and impossible to complete (See page 400.)
Koch's postulates for the acceptance of a microörganism as the specific cause of a disease: (1) the microörganism must be present in all cases of the disease; (2) it must be *cultivated in pure culture, (3) when inoculated into a* healthy susceptible animal, it must always produce the disease; and (4) from such animals it must be obtained again in pure culture.
Koplik's spots. Tiny spots simulating "white pepper sprinkled on a red background," found usually inside the cheeks, and diagnostic of measles. (See page 210.)

L

L+. The smallest amount of toxin which when injected with 1 unit of antitoxin will still have just enough toxicity to kill a 250-gram guinea-pig in four days
lyophile serum. The dry, yellow, porous material resulting from freezing pooled sera and then drying them *in vacuo* [illegible] use, lyophile

lysi[illegible] [illegible] *of fever,* in contrast to crisis

M

macule. A spot in the skin not raised above the surrounding level.

micron. A micromillimeter, the millionth part of a meter, or the thousandth part of a millimeter. Symbol μ the Greek letter mu. Example: a red blood cell is about 8 μ in diameter.

millimicron. The thousandth part of a micron or the millionth part of a millimeter.

M.L.D. Minimum lethal dose, the smallest amount of toxin which will kill a 250-gram guinea-pig in four days

Moloney test. The injection of 0.1 ml of 1:100 dilution of diphtheria toxoid intradermally; read in twenty-four hours. Positive test (erythema larger than 10 mm) indicates sensitivity to toxoid, and probable antibacterial immunity to C diphtheriæ (See pages 129, 133, 135)

morbid. Pertaining to disease

morbidity. The sick rate the ratio of the number of cases of illness to the total population.

mortality. The proportion of those who die to those who survive

N

neuronophagia. The eating up and destruction of neurones or nerve cells

neurotropic. That which has an affinity or attraction for nervous tissue

O

oliguria A diminution of the amount of urine secreted

opisthotonus. A condition due to constant contraction of the back muscles wherein the head and legs are bent backward and the body curved forward. (See page 399)

orchitis. Inflammation of the testicle.

P

pandemic. The presence of an epidemic over a large territory.

papule. A small circumscribed elevation of the skin, a raised spot.

parasite. A plant or animal living upon or within another, and at its expense.

pathogen. Any virus, microörganism, fungus, or other multiplying substance which produces disease.

pathogenic. Able to produce disease.

pathognomonic. Peculiar to a disease, and identifying it from others.

pathology. The science of the change in structure and modifications in function due to disease.

phagocytosis. The process of engulfing and destroying such foreign substances as bacteria (See page 25.)

precipitin. An antibody capable of coagulating or precipitating soluble substances. (See page 25)

prodromal. Precursory (See page 34.)

prognosis A reasoned forecast concerning the course, duration, and termination of a disease.

prophylaxis. The prevention of the development or spread of a disease.

pseudo. False

pustule. A papule containing pus.

pyogenic. Producing pus.

Q

quarantine. Formerly: restriction of freedom of movement of those who have been in contact with contagion, for the period of time during which they may be a menace to others; now a term applied to the sanitary regulations which have replaced the former restrictions.

Quellung reaction The swelling of the capsule of a microorganism caused by contact with an antiserum which contains specific antibodies against the capsular antigens

R

reactions of nerve degeneration. 1. Chronaxie Tests. Nerve degeneration, partial or total, is shown by an increased chronaxie figure in muscle stimulation; and by slow contraction and partial or no response to nerve stimulation.

2. Action potentials. The recording shows fibrillation

reagin. A specific antibody present in the blood of an atopic individual. (See page 39.)

recrudescence. Recurrence of clinical manifestations after temporary abatement.

reflexes—deep. Those elicited by percussion of tendons or bones.

—superficial. Those elicited by irritation of the skin or conjunctiva

relapse. The return of a disease shortly after its apparent cure.

S

Schick test The test for susceptibility to diphtheria. (See page 101.)

Schultz-Charlton test. A test to show the presence of scarlet fever. The intracutaneous injection of a serum specific for scarlet fever produces in a true scarlet fever eruption a local area of blanching. (See page 181)

septicemia The presence in the blood of growing micro-organisms and their toxic products, this presence being an essential feature of the disease.

serum. The clear yellowish fluid which separates from the blood as a result of the coagulation of the fibrin

Shwartzman phenomenon The rapid appearance in the skin of a rabbit, of a severe hemorrhagic necrosis at the site of an intracutaneous injection of a bacterial filtrate which has been followed, twenty-four hours later, by the intravenous injection of some of the same or various other filtrates

specific Applying to one disease only (See page 25)

sporadic. Scattered, or infrequently occurring.

S.T.D. **Skin Test Dose** The smallest amount of scarlatinal streptococcic toxin in 0 1 cc. of a solution which when injected intracutaneously in a susceptible individual will give a standard reaction.

parasite. A plant or animal living upon or within another, and at its expense.

pathogen. Any virus, microörganism, fungus, or other multiplying substance which produces disease.

pathogenic. Able to produce disease.

pathognomonic. Peculiar to a disease, and identifying it from others.

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Quellung reaction. The swelling of the capsule of a microorganism caused by contact with an antiserum which contains specific antibodies against the capsular antigens.

R

reactions of *nerve degeneration.* 1. *Chronaxie Tests. Nerve degeneration, partial or total, is shown by an increased chronaxie figure in muscle stimulation; and by slow contraction and partial or no response to nerve stimulation.*

urticaria. Hives, an eruption of the skin characterized by the appearance, usually sudden, of welts or wheals of irregular outline.

V

vaccine. An antigen used for active immunization, thus any substance used to stimulate the production of a specific resistance to an infection. Pasteur applied the term "vaccination" to all immunizations

vesicle. A papule containing a serous fluid.

virulent. Poisonous, capable of causing disease

virus. One of a heterogeneous group of infectious agents which are smaller than bacteria, and require susceptible host cells for multiplication and activity

sterilization. The destruction of microörganisms (usually by heat).

strabismus. Failure of the extrinsic muscles of the eyes to coordinate. Internal strabismus: "cross-eyed."

submorbid. Insufficient to cause manifest disease

susceptible. Not known to be immune to a given contagious disease.

symbiosis The growth together or association of two or more dissimilar organisms to their mutual advantage, such as the enhancement of their virulence.

syndrome. A group of symptoms and signs which together form a clinical picture of a disease process

T

tâche cérébrale. A red line that persists temporarily in the skin after it is stroked with a dull point. An evidence of vasomotor disturbance, occurring particularly in the presence of meningeal irritation.

toxemia. The condition resulting from the absorption of the poisonous products of bacteria

toxin. A poison produced by growing microorganisms and capable of stimulating the production of specific antibodies called antitoxins (See page 22.)

toxin-antitoxin. A mixture of diphtheria toxin and antitoxin formerly used for immunizing susceptible persons against diphtheria. (See page 130.)

toxoid. *Toxin attenuated by heat, aging, or chemicals* (See page 130)

tracheotomy. The operation of making an opening into the trachea.

U

unit (in aseptic technic). A sharply-defined zone of contamination. (See pages 439, 469.)

unit (diphtheria antitoxin). Just enough antitoxin to protect 250-gram guinea-pig from the effects of 100 minimum lethal doses (M.L.D.) of diphtheria toxin.

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A Manual of the

COMMON CONTAGIOUS DISEASES

By

PHILIP MOEN STIMSON, A.B., M.D.

[illegible]

(Middletown), and St. Francis (Poughkeepsie) Hospitals, President of St. John's Guild (The Floating Hospital), Formerly, Attending Physician, The Willard Parker Hospital, and Director of the former Poliomyelitis Service of Knickerbocker Hospital

and

HORACE LOUIS HODES, A.B., M.D.

Pediatrician-in-Chief and Director of the Department of Pediatrics Mt. Sinai Hospital, New York City, Clinical Professor of Pediatrics College of Physicians and Surgeons at Columbia University, Consulting Pediatrician North Shore Hospital, Formerly, Assistant in Pathology and Bacteriology Rockefeller Institute for Medical Research Associate Professor of Pediatrics Johns Hopkins Medical College and Director of Sydenham Hospital Baltimore

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Foreword

It is with great pleasure indeed that I announce the association with me in the authorship of A Manual of the Common Contagious Diseases, of Horace L. Hodes, M.D., Pediatrician-in-Chief and Director of the Department of Pediatrics of Mt. Sinai Hospital of New York City, and Clinical Professor of Pediatrics of The College of Physicians and Surgeons of Columbia University. An able teacher, a scholarly scientist, an experienced research worker, a talented clinician, he brings to the book wide experience and accepted authority.

In this edition he shares with me the responsibility for the many changes made throughout the book, necessitated in bringing the subject matter up-to-date. For possible future editions he will be the responsible editor and author.

Philip M. Stimson

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